U.S. FOOD AND DRUG ADMINISTRATION

SCIENCE BOARD

MEETING

Monday, October 22, 2018

9:03 a.m.

FDA White Oak Campus

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland 20993

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J. RODNEY BRISTER, PhD, MS, Temporary Member

DAVE REJESKI, MPA, Temporary Member

REBECCA SHEETS, PhD, CAPT (retired), Temporary Member

* Participation via telephone.

PARTICIPANTS (Continued)

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JEREMIAH FASANO

PETER MARKS, MD, PhD

DONNA MENDRICK, PhD

CINDY OSBORN, PhD

ANINDITA SAHA, PhD

STEVE SOLOMON, DVM, MPH

MONICA SPENCE

LEAH STITZ, MS, CFS

ALSO PRESENT:

EMILIO ESTEBAN, DVM, MBA, MPVM, PhD

CAROLYN WILSON, PhD

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P R O C E E D I N G S

MR. RAGHUWANSHI: We are going to go ahead and get started here. Before we begin, just a couple of quick announcements. If you want to attempt to connect to the public wifi -- and I say, “attempt” because I am not sure how strong or how much integrity the signal has -- you can do so now because I am going to pull this slide in just a few minutes.

Beyond that, to those on the phone, just another reminder. And we will say this constantly. Please mute your phones. Some of you are driving. We don’t need to hear the road rage. And some of you are out of the country and may have a poor connection. So please mute yourselves, and you can unmute when you want to speak.

This is being broadcast live via webcast. It is a public meeting. And, in addition to that, there is a documentary crew here filming as well that has been granted access by the agency. So if you take issue with that, now is your chance to leave, essentially. If not, then I am sure they will provide the link to their documentary, and you can see

yourselves on it down the road.

That is pretty much it. So, Mark, the mike is yours.

OPENING INTRODUCTIONS

DR. McLELLAN: Thank you, Rakesh.

Well, good morning, everyone. And welcome to the Science Board meeting for the Food and Drug Administration. This is October 22nd, and our meeting is hereby called to order.

We do have an agenda in front of us. And I will start by reminding you if we are called into decision-making, we will use Robert's Rules. The minutes are recorded. So there is no need to act on minutes. And we will start with some introductions. We will do those on the committee here around the table, and then we will shift to those on the phone. So why don't we start with Sean? And if you would tell us your name, background, appreciate it.

DR. XIE: Sean Xie, School of Pharmacy, University of Pittsburgh.

DR. TOSI: Laura Tosi. I am an orthopaedic surgeon from Children's Hospital here in D.C., and I

run our Bone Health Program.

DR. BALDI: Rhondee Baldi, an internist here in D.C. and a medical director at Inovalon.

MS. JENKINS: Annalisa Jenkins, the CEO of PlaqueTec and a member of a number of other pharmaceutical and life science and healthtec boards.

DR. PSATY: Bruce Psaty. I am a professor of medicine and epidemiology at the University of Washington, Seattle.

DR. AFSHARI: Cindy Afshari. I am from Amgen, Incorporated. I am a toxicologist responsible for nonclinical safety.

DR. BAHINSKI: Anthony Bahinski, GlaxoSmithKline, head of safety pharmacology.

DR. KOWALCYK: Barbara Kowalcyk. I am in the Department of Food Science and Technology at The Ohio State University. My background is in environmental health and epidemiology and biostatistics.

DR. STEELE: Scott Steele with the University of Rochester. I direct our regulatory science programs and associate professor in public health sciences.

DR. McLELLAN: Mark McLellan. I am the vice

president of research and graduate studies at Portland State University, Portland, Oregon.

MR. RAGHUWANSHI: Rakesh Raghuwanshi, designated federal officer for the Science Board.

RADM HINTON: Rear Admiral Denise Hinton, FDA chief scientist.

DR. BRISTER: Rodney Brister. I am a staff scientist and the chief of viral resources at the National Center of Biotechnology, National Library of Medicine.

MR. REJESKI: Dave Rejeski. I direct a program in technology innovation and environment at the Environmental Law Institute in Washington, D.C. and do largely work on emerging technologies and their legal and regulatory implications.

DR. SHEETS: Hello. I am Rebecca Sheets. I am a retired Public Health Service officer, where I served at FDA and then NIH. And now I am a consultant, and my expertise is vaccines and virology.

DR. SOLOMON: Steve Solomon. I am the director of Center for Veterinary Medicine, FDA.

DR. MENDRICK: Donna Mendrick, NCTR.

DR. WILSON: [speaking away from microphone]

DR. SAHA: Annie Saha, Center for Devices and Radiological Health. [speaking away from microphone]

DR. McLELLAN: Thank you, guys.

Yes, let's go ahead and move to the phone. And if you could identify yourself one at a time and tell us who you are?

DR. NOLAN: I am Lisa Nolan. I am a veterinarian and bacteriologist and dean of the University of Georgia's College of Veterinary Medicine.

DR. REISS: This is Ted Reiss, head of clinical research and development for inflammation and immunology in Celgene Corporation.

DR. GOLDMAN: Hi. Lynn --

DR. SARWAL: Good morning.

DR. McLELLAN: Go ahead. Lynn, why don't you go ahead?

DR. GOLDMAN: Hi. Yes. Lynn Goldman. I am dean of the Milken Institute School of Public Health at The George Washington University. And I am going to be there in about 20 minutes.

DR. McLELLAN: You don't know the parking

situation. It might take a little longer.

[Laughter.]

DR. McLELLAN: Minnie?

DR. SARWAL: Yes. Good morning. This is Minnie Sarwal. I am a professor of surgery and immunology and pediatrics at the University of California, San Francisco and Stanford University and the director of precision transplant medicine with expertise in bioinformatics and clinical trial design.

DR. McLELLAN: Very good. Well, thank you all. Hearing from all of our members, I declare we do have a quorum. So we can proceed.

I would ask that everyone take out their devices and turn them to silent. It is very important, please, and appreciate if you would take that time right now.

I want to especially welcome and thank our three expert members joining the committee for the day: Rodney and David and Rebecca. We appreciate you coming in like this on relatively short notice and participating fully as members of the committee. It means a lot to us who are permanently on the board.

So we do have a full program. We have public comments scheduled for later, and we have received written public comments that have already been submitted to the docket. The oral public comments will be restricted to 10 minutes each. And I will alert you of that timing as you approach the last 2 minutes of that 10-minute period.

So, with that, let me come back to Rakesh to talk about conflict of interest.

CONFLICT OF INTEREST

MR. RAGHUWANSHI: All right. Good morning once again. I would like to again welcome the members of the Science Board. Thank you for traveling to be here. We do appreciate it.

I would like to welcome the FDA staff who are taking part in today's meeting and also welcome the members of the public who are here today. If you need anything, feel free to alert Monica Spence. She is seated just outside this facility room in the foyer. And she will be able to help you.

Today the Science Board will hear a response from the Center for Veterinary Medicine to the

recommendations made by the board in their 2017 review of the national antibiotic resistance monitoring system program. The Science Board will also discuss potential hazards and nutritional considerations in the production of food derived from animal cell culture technologies.

All members of this advisory committee are special government employees and are subject to federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC 208 is being provided to participants in today's meeting and to the public. FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Based on the agenda for today's meeting, no conflict of interest waivers have been issued in connection with the topics.

We have one open public comment period scheduled for 3:30 p.m. with 5 members of the public having signed up to speak.

For our members on the phone, please remember

again to unmute when you are speaking and mute when you are not speaking to help minimize any background noise and so the transcriber can pick up all that is being stated.

Every time you speak, I will ask that you state your name, even if you are seated around the table, so that our transcriber can easily take note of that. I ask that you speak clearly and that you don't allow your voice to trail at the end of a sentence or at the end of your comments so that every word can be picked up for the transcript.

Next to the transcriber, at the table where I am pointing with my pen is a chair for our speakers who are not seated around the table. If you are seated around the table and you have a scheduled topic to speak on, we can pass you the clicker and you can speak from your seat. But for other speakers who have been invited, I ask that you please sit at the speaker's chair, and we will make sure you get the clicker. It is very simple, backwards and forwards. And I will get your slides loaded from up here.

With that, thank you all once again for

coming. And we look forward to a very productive meeting.

DR. McLELLAN: Okay. For those of you who are members here and are sitting around our table, we use our usual practice. Cynthia has got her hand on her label right there. When we go to wish to speak, we will raise our flags. And you will be recognized in the order taken. Those of you on the phone, just please interject with your name, and we will recognize you and proceed from there.

So, with that, let's go ahead and start. We are pleased to have with us Rear Admiral Denise Hinton, who is FDA's chief scientist. And she will be giving us an update and report. Glad to have you here, Denise.

RADM HINTON: Thank you.

CHIEF SCIENTIST'S UPDATE

RADM HINTON: Good morning. Thank you to all of our Science Board members for traveling to be here today, and thank you to those on the phone for your time and commitment. And a special thank you to our temporary members who are expert members at that who

are joining us today and providing their valuable expertise in the area of cell cultures. We appreciate your service.

A lot has transpired since we last spoke in April. And so I would like to give you some highlights of the work we have been doing here in the Office of the Chief Scientist. As you know, supporting our scientists is important to me, important to us. And last fiscal year, we put on 29 training events for almost 3,500 participants and awarded close to 700 continuing education units. We conducted six FDA grand rounds for almost 3,000 attendees and awarded over 650 CE units. Some of the grand rounds were picked up by major media outlets and serve as a great way to showcase our FDA science. These include topics like 3D printing, the role of modeling and simulation in regulatory pathways and tobacco product standards. We presented our annual scientific achievement awards to our very best FDA scientists for their work in areas such as development of a novel method for determination of sulfite in foods, outstanding scientific review of regenerative medicine, therapy and tissue-engineered

products that have unprecedented regulatory challenges in cell therapy, and work in whole genome sequencing to support key regulatory decisions. Those awards were partly sponsored by members of this board. So I thank you for your time in helping to make those selections. These efforts work towards fulfilling the HHS strategic objectives of expanding the capacity of our scientific workforce to support innovative research.

In an effort to educate our scientists on the issue of predatory publishing, my office launched an educational campaign to describe what it is, what constitutes a predatory publisher, and why scientists should be careful when engaging with predatory publishers or participating in predatory conferences. We want to protect our integrity.

Our Senior Science Council added two new working groups. One is the Research Impact Working Group, and the other is Additive Manufacturing Working Group. The Research Impact Working Group aims to develop metrics and ways to qualitatively assess the impact of our regulatory science research, while the Additive Manufacturing Working Group provides a forum

for scientists across the agency to come together to discuss developments in this very important and quickly evolving field so that the agency keeps pace with scientific progress.

Our Tech Transfer Office had three new CRADAs; that is, cooperative research and development agreements, which completed 21 invention reports, 15 patent applications, and got 18 patents issued along with 3 new technology licenses in the last year. I bring this up just to highlight that we do a lot in great, innovative scientific activities being conducted here at the agency.

Our health informatics group worked to further its Healthy Citizen, the pilot program, which gives the FDA the ability to provide customized patient information via a safe and secure tool that does not share or provide personally identifiable information in the mass of patients. We issued an emergency-use authorization for the Department of Defense's use of freeze dried plasma to support and deploy military personnel while happening to facilitate FDA's response to Ebola in the Democratic Republic of Congo and Zika

in the Americas.

Our engagement with the external scientific community also progressed tremendously well. Through our broad agency announcement program, which allows the agency to tap into external knowledge and infrastructure, we made 40 awards totaling $40 million. Extramural research funded through this broad agency announcement has been or is being conducted in areas such as supporting field lab testing of Ebola antibodies, development of organs on a chip or microphysiological systems, optimizing the use of opioid therapy following surgery, and comparative surveillance of generic drugs by machine learning.

We also released our predictive toxicology roadmap and hosted a part 15 public hearing in September to engage our stakeholders and get their suggestions on how to foster the development and evaluation of emerging toxicological methods and new technologies and incorporate them into regulatory review.

My office oversaw the agency’s engagement in multi-agency efforts to study the full range of

potential health effects from BPA. In particular, the National Center for Toxicological Research, NCTR, conducted a core study over two years in which they studied potential toxicity in rats. This was conducted in accordance with federal regulatory and statutory guidelines for toxicity testing. They did a very meticulous and diligent job in completing this study and provided valuable information to the National Toxicology Program in public as part of the Clarity BPA Program, which also includes the academic sector.

The Office of Minority Health has continued its important outreach and efforts. They participated in Inaugural Rural Health Symposium, which provided a forum for the FDA and key stakeholders in rural and tribal communities to discuss ways to work together to address the critical and unique health challenges these communities face relative to the opioid crisis, tobacco use among youth, and telemedicine, to name a few. These activities and efforts are some of the ways that my office and this agency work to fulfill he strategic goals of the strategic plan, including to protect the health of Americans where they live, learn, work, and

play.

I will close by saying a couple of more things. I am very proud of our scientists and the dedication that they have to our mission. It is an honor to support them and represent them at various meetings, including this one.

FDA is a great place for scientists to build a career. So if you know of anyone interested in the medical product regulation, please ask them to consider FDA.

I want to give a special thanks to Dr. Lynn Goldman and Dr. Bruce Psaty. They are both long time members of the Science Board. And because of term-limit rules, they will be stepping down at the end of this year. We hope to have them back in the near future. And over the years, Bruce and Lynn have been very vocal and hardworking members of the board, so helping with various subcommittees, including as chair of several, and asking poignant questions during these meetings.

Bruce has also served as chair of the Science Board a few years ago. And I know that Rakesh in

speaking enjoyed working with both of you and getting to know you over the course of the years. So I echo his sentiments. And then I hope that you will consider serving again in the future.

Thank you all again for your time, your service, your thoughts, ideas, and opinions. And I look forward to a robust and productive discussion today. Thank you.

DR. McLELLAN: Thank you, Denise.

Are there questions for the chief scientist?

DR. STEELE: Thank you, Denise. Just a quick question. Exciting to hear about all of the work underway. I think it came up at the last meeting there was some discussion about FDA proposing to create an intramural research training program, with the NIH.

RADM HINTON: Yes.

DR. STEELE: I was just curious if that is something that is still underway or being considered.

RADM HINTON: Yes, it is still underway and being considered. As a matter of fact, Leslie Wheelock, the director of the Office of Scientific Professional Development, we are still in discussions

amongst the agency and with external parties to get that initiated. So you can quote me on this. However, it might take some time. I will caveat it with, you know, it may be extended a little bit. But we are hoping within by FY2020, we will have it underway.

Thank you.

DR. McLELLAN: I will add one question, Denise. We spent quite a bit of time over the past years looking at employment and the challenges of getting strong employees into the FDA. Can you give us any sense of progress in that? And, you know, it has just had some hurdles in the past.

RADM HINTON: Yes, we have had some hurdles in the past. And it is something that we have been fully committed to addressing. We actually have a scientific workforce that has been putting into place a team that is working to help expedite the hiring of scientists within the agency. And I think just recently, we did have an announcement or policy that we put in place that week and have direct hiring authority for some key positions. And I believe that may be posted on fdajobs. So we have done quite a bit to

progress in this area.

MR. RAGHUWANSHI: And I will add one thing to that. The FDA is approaching hiring in a novel way. If you live in the D.C. metro area, you may have noticed advertisements that FDA is hiring on the Metrobus and at bus stops as well.

RADM HINTON: I think you may have seen Dr. Gottlieb tweet that on the Twitter account.

DR. GOTTLIEB: If I can, I will just comment on that briefly. And thank you, Denise. Denise is providing a lot of leadership to what we are trying to do with respect to recruiting and retaining talented scientists and clinicians here at the agency.

I think that the challenge right now -- and I have sort of an historical perspective having been here in two different iterations. I think in the past, there was a challenge in trying to recruit top-flight scientists and clinicians to the agency. You know, salaries were very competitive outside the FDA. You know, people were sometimes reluctant to make the jump from academic careers or even careers in industry to come to the agency. I think we are at a point now

where we have more authority to be somewhat competitive. And there is much more interest that I am seeing. I think the senior leadership is seen among top-flight clinicians and scientists who want to come into the FDA, even young talent wanting to come into the agency, recognizing that this is an exciting, rewarding place to work.

So we are seeing good candidates. The challenge I think is still the hiring process itself. The mechanics of the hiring process and the on-boarding process can sometimes be so long and so difficult that sometimes we lose good candidates. If someone is looking to make a job change from an academic career, even from industry, and they are weighing going into the FDA versus taking another job in another sector and it takes us 8 months or 12 months to onboard them, by that time, they might have found another opportunity. So that is the biggest challenge right now.

We are actually -- I think we are seeing the talented people who are excited about the prospect of coming to work for FDA. That is the good news. The bad news is that we still have a challenging hiring

process that we are making strides to fix. I think the direct-hire authority and some of the cures authorities are going to give us very robust tools to address that among certain cohorts of people that we hire to the agency, particularly clinicians and the scientists. So I am optimistic that we are turning a corner there.

DR. McLELLAN: And of course, that gives us a nice transition. Commissioner, we are glad to have you here. We are anxious to hear about your priorities and progress and how your term has been going so far. So thank you, Scott. Appreciate you being here.

COMMISSIONER'S UPDATE

DR. GOTTLIEB: I think it has been going pretty well. I appreciate it.

I just wanted to start out. I want to thank Denise and everyone here today for your support. And I want to just echo Denise's sentiments about the two Science Board members who have reached their term limits: Bruce and Lynn. We appreciate very much the contributions that you have made to this board and to the agency and hope to continue to work with you in different capacities. They have been long-serving

members of the Science Board and work very hard to provide the agency with very good advice over the years. And I am grateful for their contributions and their service. And we hope we can get them back in some capacity in the future.

Since we met last April, we made a lot of progress, I think, on the topics that we have talked about in the past, particularly antimicrobial resistance and the use of cell culture technology. Those are topics we brought before the board briefly before. I want to highlight them today. I know they are going to be the focuses of a discussion here.

I would like to just start out, if I may, just talking about some of the policy priorities that I am thinking about right now and then transition into a discussion of some of what we are doing with respect to antimicrobial resistance and cell culture media. I just want to touch on three of the priority areas that I have talked about in the past: e-cigarettes and tobacco use generally, what we are doing to confront the opioid addiction, and some of the steps we are taking to try to address the market for drug pricing

and trying to create more competition and facilitate more access to drugs for consumers. These are obviously areas I have spent a lot of time talking about from the first day I got here. And I think that we are going to be transitioning how we approach some of these challenges into 2019. I just want to highlight some of our current thinking for the board so you know what I am thinking about, where I am focusing my time.

On the e-cigarettes, when I came aboard, early after I came aboard, we unveiled our comprehensive plan with respect to the regulation of nicotine in combustible cigarettes. The effort was to try to render combustible cigarettes minimally and non-addictive and more rapidly transition adults off of combustible tobacco, onto modified-risk products, hopefully off of nicotine altogether; if they don't want to quit nicotine altogether, preferably onto nicotine-replacement therapy, medicinal products that are available without a physician's prescription. But for adults who still wanted to get access to satisfy levels of nicotine without all the harmful effects of

combustion, we saw the electronic nicotine-delivery systems in e-cigarettes, in particular, as a potential opportunity to offer the same access to nicotine without all the health effects of combustion, not risk-free. We recognize there are risks associated with the e-cigarettes. And they need to be put through a proper set of regulatory gates to properly assess that, but there is a presumption that they are less risky than combustion. I think it is a fair presumption.

We said all along that our accommodation to take more time to put the e-cigarettes through an appropriate series of regulatory gates at the same time we were moving to regulate nicotine in combustible cigarettes couldn't come at the expense of addicting a whole generation of youth on nicotine through the e-cigarettes, that the allowance we were making to maintain these products on the market while we put in place the parameters on how we would regulate them couldn't come at the expense of youth taking up these products. And the industry needed to be vigilant with respect to that. I said that at the outset when we announced the policy last summer, and I probably if

someone went through the transcripts have said that dozens, if not 100, times in the intervening months.

We now have evidence, as many of you know, from the National Youth Tobacco Survey of nothing short of what I think is an epidemic in the growth of e-cigarette use among youth. And we are going to need to step in to address that. We will be stepping in very shortly to do that.

Just to give you sort of a sense of where we are thinking, we have a problem with appeal, and we have a problem with access. These products are too appealing to kids, and they are too accessible. And so with respect to appeal, one of the things that makes them most appealing is the flavors. And we are looking to see how we could regulate the flavors and access to the flavors.

With respect to access, we know children are accessing these at convenience stores primarily. The online sales aren't that robust right now, although they are getting them online as well through store purchases, we believe, but a lot of the sales are through convenience stores. And we, in fact, did an

undercover operation where we targeted stores for selling e-cigarettes to kids. We expected based on the resources we were putting against that operation to come out with 300 warning letters. We came out with 1,300. So it is just rampant, sales to kids among the convenience stores, at a scale that exceeds what we believed was going on. And I do believe that there is a presumption when the clerk's inside the gas station of the convenience stores that they might be reluctant to sell combustible cigarettes to kids, but somehow they see it as more acceptable, appropriate to sell the e-cigarettes. And we have got to pierce that. We are going to be taking steps to see how we might restrict access to certain of the e-cigarettes, particularly the flavored products, as a way to address that.

On the issue of opioids, we all saw the recently passed legislation, a bipartisan legislation, that gave the FDA really a robust set of authorities and new tools to address the opioid crisis in some novel ways. These were authorities that the agency had long sought that are baked into this bill the President is going to reportedly sign this week. We are going to

make quick implementation of certain of these authorities once this bill is enacted, particularly the authority with respect to blister-pack and the immediate-release formulations of the drugs and the authorities with respect to developing evidence-based guidelines on prescribing.

We still believe that one of the primary roles for the agency is to try to address exposure to opioids in a clinical setting. We know that if we can reduce exposure and try to rationalize prescribing to make sure only properly indicated patients are getting opioids and they are getting them for a duration of use that comports with the clinical circumstances in which the drugs are being prescribed, we can reduce exposure and, in turn, reduce the rate of new addiction. We know a certain percentage of patients who are exposed to opioids in the clinical setting will develop a dependency and some proportion will go on to develop addiction.

It is declining because, more and more, the new addiction is being formed outside the medical setting, in the illicit setting, but the medical

setting is still a place where people are exposed to opioids and go on to use them in an illicit fashion. So we are going to be looking at how we can blister-pack the IR drugs in packs that comport with what the appropriate dispensing should be. And in many cases, that is one or two days for a lot of post-acute surgical procedures: laparoscopic cholecystectomy or appendectomy. Our data shows that the proper dispensing should be one or two days, even for partial mastectomy. Our data shows two or three days for a procedure like that.

We are going to be working with the National Academies of Medicine and provider groups to develop evidence-based guidelines on what the appropriate course of therapy should be for some common post-acute indications. This is very different than consensus guidelines. The CDC is working on consensus guidelines, which are basically expert opinion based on the available knowledge. We are going to be working on trying to develop new evidence, either through a retrospective or prospective analysis, on what the actual utilization is in these indications so we can

have evidence-based guidelines that could potentially be incorporated into drug labeling as a basis for trying to better rationalize prescribing.

We are also going to be talking a lot more this fall and going into next year about not just making sure that prescriptions are only written for appropriate circumstances and the number of pills dispensed are appropriate for the indication for which the prescription is being written but talking more about morphine equivalence and the strength of the prescription that is being written.

This matters. There is data that shows that MME, which is the morphine equivalence that someone is prescribing, does speak to the propensity to develop dependency and addiction. There is data suggesting that people who are started on higher doses are more likely to develop dependency and more likely to develop addiction to the opioids. And so to the extent that we now know that that is true and we are going to help develop some more evidence around that, we also need to think about that as a variable in how we address this crisis and how we educate physicians. And so that is

going to be a topic going into the fall.

Just on drug pricing briefly, we have talked a lot about this over the past year in the national drug competition action plan, a number of initiatives. One of the things that we are going to be talking about going into the fall is just trying to address issues around some of the challenges that the generic drug industry is facing. They are facing issues around rising cost of goods, declining reimbursement. Some of these fall well outside the FDA's purview, but there are things that FDA can do to help I think facilitate a healthier environment for generic drug competition. It starts with I think trying to facilitate more of what the generic industry often refers to as high-value opportunities, the ability to genericize things like complex drugs, drugs with REMs associated with them, drugs with complex formulations.

There have been historical challenges with genericizing those compounds. Those compounds also represent some of the higher-value opportunities for the generic industry, the higher-margin opportunities. They also represent a big public health opportunity for

consumers. To the extent that a lot of those hard-to-copy drugs remain branded drugs in perpetuity, it denies consumers the competition and the affordability that would come from brisk generic entry when patents and other exclusivities have lapsed in those drugs. So we are going to be focusing a lot on trying to facilitate those high-value opportunities.

We are also looking for ways that we can help facilitate more efficient generic drug development to help lower the cost of goods. And you saw an announcement last week that we are working with the IHC to try to harmonize global standards for generic drug applications and generic drug filings to try to move towards what we hope is a global application process for generic drugs. We might not ever get to a truly global application, like the common application for college admissions, but something that is more akin to a very similar process across developed markets, where if a company develops a generic drug for the U.S. market, they can more easily file in the EMA, in Health Canada, and with the Japanese authorities so that they can enter multiple markets simultaneously. We see

cases where there are generic drugs available in Europe that we would like to see that competition in the U.S. We also have cases where our generic manufacturers here penetrated our market but have a difficult time penetrating the European market. And I think the more level playing field for the filing of applications can create more competition that will ultimately benefit consumers.

I just want to briefly -- maybe I will pause and see if there are questions and then turn to the topics of today if that is okay. How much time do I have?

DR. McLELLAN: As much as you would like.

DR. GOTTLIEB: Thanks a lot.

DR. McLELLAN: Thank you.

Are there questions by the board?

[No response.]

DR. McLELLAN: While you are thinking, members, I will make a comment. Commissioner, for those of us on the board that spent an amazing amount of time on the opioid issue, it is really gratifying to hear your progress and hear the movement on that. It

is something that many of us have felt very passionate about and really, really excellent to see that.

Comments? Yes, Lynn?

DR. GOLDMAN: Good morning. I really enjoyed hearing your overview of the things that are going on. And to me, it is just all public health, public health, public health. And so it makes me feel really good about the direction where you are taking the FDA.

I wanted to mention something you didn't mention but to really compliment the FDA on having taken action on the color additives that are in a lot of our children's food and candy products and so forth. It was really great to see FDA taking such decisive action. I know I am not the only one in the pediatric community who really appreciates it. Thank you so much.

DR. McLELLAN: Barb?

DR. KOWALCYK: Thank you. Barb Kowalcyk.

So I wanted to just follow up. I think FDA has a lot on their plate. And one of the things that I didn't hear that I wanted you to comment on is the efforts that FDA is taking to implement the Food Safety

Modernization Act. Foodborne disease is a serious public health issue. And I just wanted to take this opportunity. I didn't hear it as one of the priorities for the agency going forward. And there are some significant parts of FSMA that still need to be implemented. And I just thought maybe you could comment on that.

DR. GOTTLIEB: Yes. No. Sure. And it is a top priority of the agency. I was touching on some of the issues that I outlined when I first came aboard, which, you know, arguably, were some of the policy issues that are very paramount then and continue to be paramount now.

But FSMA remains a top priority. And I spend an extraordinary amount of my time working on food-related issues to try to drive these things forwards, not just FSMA but some of the unfinished agenda with respect to menu labeling and the unfinished agenda with respect to the nutrition facts panel, trying to make sure that we get those firmly in place. We obviously got menu labeling over the finish line. We still have some work to do with respect to the nutrition facts

label, the modern label, making sure that is fully implemented. And we have unfinished business with respect to FSMA.

I think that, you know, my view of FSMA implementation right now is it is on track. And I am heartened by the progress that we are making. And I think it is going to be transformative with respect to how we approach food safety overall. But I think that the issues that we have left that are on the table are the hard issues. And that is why they are still on the table. You know, this has been a piece of legislation that has been under implementation for many, many years now.

And the sort of issues that -- I don't want to say got pushed off but the issues that remain at the end of that long process are the ones that are more challenging. How are we going to implement the agricultural water standards, for example, is a key issue. That is a difficult issue for the agency, and it is a difficult issue for farmers, especially recognizing the diversity of how different farmers get their water in different regions of the country, you

know, the same rules that apply to, you know, the Southwest or the Southeast aren't as easily applicable to the Pacific Northwest, where farmers trade water sometimes on a weekly basis and don't know exactly where their water is going to come from next week. And so implementing the same testing standards there you might implement in other parts of the country sometimes is onerous and maybe even insurmountable. And so we need to think of how we are going to take a flexible approach that accommodates the different ways that agriculture is practiced in the country.

That is just one example, but there are other examples of elements of that law that I think will continue to be not insurmountable but challenging. And there is a lot of folks working on it, including myself, to make sure that we get this fully across the finish line.

DR. McLELLAN: Sean?

DR. XIE: Yes?

DR. McLELLAN: Please, I will remind everyone to give your name first. Thanks.

DR. XIE: Sean Xie, School of Pharmacy,

University of Pittsburgh. Thank you, Mr. Commissioner, for the very impressive update. I want to follow the discussion Mark raised about the opioid prescription drug. We studied some of the drug-drug interaction, including the prescription oxycodone co-administration with diazepam. These two drugs used together caused a serious death in the clinic.

So I was curious because last time, one of the scientists presented this initiative we have built up to build a lot of data for sharing total to allow scientists to analyze, to understand the how and the why there was a poly-drug or drug-drug interaction will cause a serious death related to opiate prescription drug.

So including our School of Pharmacy, we have a center funded by NIH, it is a computational drug-based research center. So we can access a lot of the data to use in machining to learning artificial intelligence to analyze in-depth why the clinical outcome can be expert interpreted through the system of pharmacology. So have you any initiative to build through this direction?

DR. GOTTLIEB: We would be very interested I think in access to tools and capabilities that would allow us to better understand this. I don't know precisely what is going on at the review level. I know that this has been an area of work. I would be happy to follow up with you directly because I would like to have the dialogue around places where we can continue to build out our knowledge around this.

Obviously we have labeled the products to contraindicate concomitant use of the benzodiazepines and opioids, recognizing, you know, the unique safety issues. But we still see concomitant prescribing of those two compounds.

I think that going forward, you know, there are going to be better tools for trying to address this, particularly with respect to the implementation of electronic prescribing. As you know, the new legislation mandates fully electronic prescribing in Medicare Part D I think by 2021. Once you have Medicare requiring electronic prescribing of opioids, I think that is going to drive the rest of the market along. And, you know, having fully electronic systems

will help facilitate props and, you know, impediments that could restrict, you know, concomitant prescribing of drugs that potentiate the dangerous effects of opioids.

There are other compounds where we have work going on looking at the risks associated with dual prescribing. Another one I am thinking of is the gabapentinoids, where there is some concern about the potential for abuse with respect to the gabapentinoids, particularly in respect to co-prescribing with opioids, where there is some belief that it could be being used in a recreational manner, given the patterns of prescribing that we have seen. We are certainly still investigating that. So I don't want to draw any conclusions here today. But, you know, to the extent that the tools that you are working with and developing probably could have applicability outside just the benzodiazepines it sounds like can help us look at other concomitant prescribing that could be potentiating abuse and addiction, we would be very interested to hear about that.

DR. McLELLAN: Annalisa?

MS. JENKINS: Annalisa Jenkins. So I would like to applaud the work that you have been really championing on the ability to access low-cost options to patients, including the work on generics.

I was interested in your comments on securing access to these important medicines in light of recent challenges in the global supply chains as it relates to quality and recognizing the historical practice of a significant degree of importation of these medicines. I just wondered if the FDA has particular work ongoing as it relates to policy and regulation to ensure that you can enable sustainable access to high-quality generic medicines for the U.S. population.

DR. GOTTLIEB: Thanks for the question. There has been a shift over time. We are going to put out data on this soon to illustrate this. There has been a shift over time, not just of manufacturing ex-U.S., where a lot of the generic drugs are manufactured outside the United States, but also a shift in our oversight resources, where much more of the inspectional focus is now ex-U.S. marrying the migration of the manufacturing to markets like China

and India. And so there is an emphasis on making sure that we have a proper footprint and are providing equivalent oversight to those ex-U.S. facilities. It is not without challenges. There is no question about that. But we spent a lot of time trying to structure the field force through the reorganization that we have undertaken over the last two years to give it a better framework for doing more inspections outside the U.S. with what we have done with respect to program alignment.

I do think that, you know, we have also talked about trying to build out a framework for drug and greater use of continuous manufacturing as a way for the industry to manufacture new drugs, not just with respect to novel drugs but also generic manufacturing as well. And we are having a robust discussion with the generic industry about how they can make use of continuous manufacturing platforms, rather than the batch-type manufacturing that we now see in the generic industry, which is very expensive, very time-consuming, and not without risk. A continuous manufacturing process cannot just be lower-cost and

potentially more robust but potentially lower-risk as well.

I think one of the virtues if we are able to make that transition, if more manufacturers are able to make that transition, is we could see the redomestication of manufacturing. And, in fact, we have got a big ask in the budget to try to get resources to try to create a regulatory framework so we can drive more conversion to continuing manufacturing. One of the primary arguments we have made from a policy standpoint was that this could lead to more domestic growth of manufacturing capabilities for drugs because the continuous manufacturing platforms tend to be small footprint, you know, small resources in terms of human capital, but they require highly skilled human capital. So it is exactly the kind of manufacturing footprint that you would want to maintain, if you were a company, you would want to maintain, tight control over and have in a more developed marketplace. You wouldn't necessarily want to move it offshore because the labor inputs are a lot less with these platforms. And the skilled labor inputs are a lot higher.

So we think that as -- it is not necessarily the reason for doing it. There is a lot of public health rationale for doing it. But we think as we are able to convert more of the industry to embracing these kinds of platforms, we are going to start to see more manufacturing come back to the U.S. and other developed markets, where, you know, presumably we will be able to maintain closer regulatory scrutiny because they are collocated with the agency here in the U.S.

But I will end by saying we have shifted a lot of our resources, our inspectional resources, ex-U.S. for precisely the reasons you seem to allude to, that need to maintain the quality of the products that are being imported, both the finished products as well as the raw API. And the data we are going to put out is going to demonstrate that.

DR. McLELLAN: Sean, do you have a follow-up question? No? Okay.

Let me ask those on the phone, since we have the commissioner here, do you have any follow-on comments for him?

DR. REISS: Yes. Hi, Mark. This is Ted

Reiss. I just have a question.

So at one of our last meetings, we had a discussion about reenvisioning sort of the clinical research, clinical development process, had a whole discussion about blockchain and the implication there. Has any further work, Commissioner, been done along those lines, either with that technology or other technologies about reenvisioning the development process?

DR. GOTTLIEB: I think the place where we are looking at blockchain technology is some of the supply chain issues that we grapple with, first and foremost, not just on the food side of the house but also on the drug side of the house with respect to implementation and Drug Quality Security Act. We recently announced that we are hiring into the agency as a deputy commissioner Frank Yiannas, who is really one of the thought leaders and pioneers on the use of blockchain in the setting of food security and securing the supply chain with respect to food, but I fully expect Frank to have a broader mandate to look at how we can apply that technology not just to ensuring the safety of the food

supply chain but also other supply chains, particularly on the drug side of our house as well, where we face challenges, obviously, and have certain obligations under DQSA to implement some new technology to secure the drug supply chain.

So I think Frank is going to take a leadership role out of his new office in thinking about how we can make wide use of this technology. And it was one of the attractive virtues in recruiting Frank into the agency, was recognizing that he was going to be able to help drive use of this technology potentially forward for us.

DR. McLELLAN: Any other comments from those on the phone?

[No response.]

DR. McLELLAN: Commissioner, I will just add a comment on the blockchain. We have been involved with a fair amount and fully agree the supply chain is a great place to implement. One might envision the holy grail, though, being medical records and, of course, a huge lift there to attempt to move it in there but certainly an extraordinary opportunity for

the future down the road a bit.

DR. GOTTLIEB: I think on the development side in thinking about how to use blockchain with the transfer of information in the drug development process, I think whatever we do there is going to have to be in concert with the provider space and with CMS as well because it is going to potentially impose burdens on the providers or onto the healthcare system more generally.

But it is something that we have thought about, and so I know some of the CROs are looking at it as well. But the most efficient way to think about how to deploy the technology isn't just within the sort of now construct of a clinical trial environment but doing it more broadly in the healthcare environment.

If I might, I just want to touch on antimicrobial resistance and cell culture media because I know you guys are talking about it today. On the issue of antimicrobial resistance, I know this group has had a lot of discussions. And the input that we have received from you has been very helpful.

We launched very recently, a couple of months

ago, a broad strategic plan that encompassed across all of our centers how we are going to support antimicrobial stewardship in the veterinary setting; how we are going to drive the development of better antimicrobials in the drug setting; better diagnostics in the medical device setting; really, how we are going to address the issue of antimicrobial resistance across our entire portfolio. The comprehensive approach that we announced had four major elements to it, four components, if you will, across the whole continuum of product development and use of antimicrobials. First, we are facilitating the product development to ensure a robust pipeline of better, targeted treatments to combat multi-drug-resistant organisms.

Second, we are taking new steps to promote antimicrobial stewardship, careful stewardship across both the human and animal health settings. We know from our work to date, it can help preserve the effectiveness and the availability of the drugs that we have in our armamentarium today and help potentially slow the development of resistance.

Third, we are supporting the development of

tools that can help facilitate better surveillance of antimicrobial use in determining when pathogens have developed resistance. It isn't just tools on the diagnostic side of our house but also tools on, for example, the animal health side of the house, better surveillance, better tracking of data in that setting to develop better information about patterns of emerging resistance.

And, finally, we are advancing scientific initiatives to help all stakeholders answer questions related to antimicrobial resistance, really trying to foster a dialogue, including research that can support the development of alternative treatment approaches. These can include bacteriophages, live biotherapeutic products, other kinds of technology, new technology that can help address these challenges.

At the same time -- I will just close here -- we are also thinking a lot about how we can change the reimbursement paradigm for drugs targeted to multi-drug-resistant organisms. I think that we have had challenges, just historically, from a structural standpoint with respect to trying to develop drugs that

you don't want to use in a model of reimbursement, where innovators are paid based on how many times a new innovation is used. In this space, the economic model that we use to reward innovation is sort of directly antithetical to the kind of stewardship that we want to apply to any very effective new drug that could help target multi-drug-resistant organisms to where the imperative would be to hold such a drug in reserve.

So we are looking at and having discussions with CMS and other stakeholders about what alternative reimbursement models could emerge, ne of which that we are looking at very actively is a licensing model, where institutions might pay a licensing fee, a flat licensing fee, similar to how they buy software for access to a drug that they can then hold in reserve. You can envision licensing fees being based on the size of an institution or the number of beds a hospital might have. There might be some supplemental fee above a basic licensing fee for the number of times you use it, but the licensing fee would provide for sort of a base of reimbursement that could help create a predictable market for anyone trying to enter the space

and the entrepreneur entering this space.

On the cell culture technology, which I know is going to be the topic of discussion here today -- and we appreciate the dialogue very much and the opportunity to bring this issue before you. It is a new issue. It is going to be a challenging issue as we move forward. We are also having a public dialogue at a meeting that we are hosting this week in conjunction with the USDA. We see a lot of promise from this technology. We think that there could be a lot of advantages to producing different meat products in a cultured environment.

We are very familiar with this technology. The technology itself really came out of the drug side of our house, where people were using culturing technology to try to develop tissue for transplantation and for human use. And they were also obviously using similar culturing technology for the development of certain biological drugs. And entrepreneurs recognize that these same tools could potentially be applied to the development of meat products that could be used for human and animal consumption.

Initially the costs were prohibitively expensive for this to be used on a wide-scale basis. In fact, the products that we have seen in development right now are sort of more of the spoke meat products, if you will, you know, very high in foie gras and things like that. But, technology being what it is, the costs are coming down quickly. And we think we are just probably a couple of years or several years away from the opportunity to see meat products that could be more widely available for either human or animal consumption.

So it is very important that we think through what that regulatory landscape is going to look like right now. And it is very important that we think through these issues in conjunction with our partners at USDA. I think that we fully envision a role for USDA.

I have had many private discussions with Sonny Perdue about this, about what our regulatory paradigm could look like where there is some joint jurisdiction. We share jurisdiction with USDA and a lot of other places. Clearly in this setting, fish

products, which probably are going to be the first products out of the gate, are going to be clearly in the jurisdiction of FDA. Animal food products will be clearly in the jurisdiction of FDA. Other meat products will. But with respect to meat and poultry, where USDA has historically played a role, there will probably be some opportunity for shared jurisdiction with USDA and some role for USDA in the later stages of the marketing and commercialization process and maybe elements of the sort of finishing process, if you will.

We are thinking about what the lexicon is. We have been talking about this. What is manufacture in this context? What are sort of, you know, the final stages of finishing the product? What constitutes marketing and labeling in this context? I think getting the lexicon right, getting the language right for how we talk about, you know, the regulatory framework for these products is going to be very important to trying to, you know, figure out what the policy is and adhere the policy to the science here. So I hope that is something we can all talk about today, where we are having a robust discussion about it

internally at FDA, but we have an opportunity now to get this right, do it in advance.

I think very often historically, we have been playing catch-up to new technologies, sometimes stepping in to sort of regulate after the fact. And that is always hard. It is always hard to try to develop regulatory parameters and apply them after an industry has already grown up. I think this is one place where we have the opportunity to do it a priori before these products are widely available in conjunction with other regulatory partners, in conjunction with the industry and other stakeholders as well. The industry and the stakeholders who are making investments here are coming to us asking, you know, pertinent questions about how these products are going to be approached by FDA, recognizing that they are going to need to clear a premarket regulatory process. And so we have an opportunity now to work across multiple stakeholders I think to get this right.

So we are very grateful for your input today. This is an important issue. I have spent a lot of time on it. It is going to continue to be an important

issue going forward. And I think that coming out of this meeting today, coming out of the dialogue that we are having in conjunction with USDA, the public meeting, we are going to go back with our USDA partners and try to work on, you know, a comprehensive policy framework for how we would address the meat and poultry, in particular. We know how we are going to address everything else -- that is within FDA's scope of jurisdiction -- but with respect to the meat and poultry, in particular, how we are going to address that in concert with USDA, where the jurisdictional lines are going to be, what makes sense to fall in their purview versus ours, and how we can continue to apply our expertise to make sure these products aren't just available for consumers but are also safe and meet our public health standards.

So, with that, I would like to close. I wanted to thank you for your assistance on these issues today. These are important issues that we are all grappling with.

Any questions?

DR. McLELLAN: Any questions for the

commissioner? Commissioner, we are so -- oh, we do have a question. Sorry. I didn't see you.

MR. REJESKI: Just an interesting comment because there is an intersection between the two topics you talk about. We did a bunch of focus groups trying to understand how people feel about cellular agriculture, cultured meat. And we put a bunch of benefits in front of them, and one was nutritional enhancement of the meat. We could put more B-12 into it, iron, and stuff.

One of the things that people really got excited about is dealing with antimicrobial resistance. That was a very interesting thing that quite often people even brought up. They kept sort of talking about, "Is this a way of moving out? I brought massive amounts of antibiotics that are used prophylactically in livestock and poultry out of that system." And that was something that kind of surprised us. And people came back to it again.

So there may be some -- you talk about the lexicon. How do you talk about this? It might be an interesting way of shaping it or framing it.

DR. GOTTLIEB: We haven't done surveys, but we think this is, you know, a potentially big opportunity and that there could be public health advantages to developing certain products in this way, not just with respect to the ability to guarantee, you know, consistent nutritional value, the ability to be able to more easily certify that certain additives aren't included. You know, when we have looked at this and had discussions with consumers, they see certain environmental opportunities from these products.

So we see a lot of opportunity here. And I think that from my standpoint, you know, my concern is that we make sure that we get this right and delineate a regulatory process that is clear, that has bright lines, that is accessible so that we don't stall this opportunity. I think we are right at an influxion point of a vast new area of technology. And, you know, we have been at the sort of precipice before. And sometimes we have got it right, and sometimes we have got it wrong. And we have seen technology stall as a result of, you know, regulatory and policy approaches that got it wrong. And I want to make sure we get it

right.

You all read the same newspaper as I do. You know this has been an area of intense political scrutiny. And there are a lot of groups lined up on both sides of this issue, particularly the side expressing some concerns about what this could mean for traditional agricultural processes. You know, I don't think one has to come at the expense of the other. I think we can develop a policy process that provides an opportunity for both and helps consumers see the advantages of different products. But I do think that we need to, you know, be vigilant about making sure that we define a process here that doesn't forestall this opportunity for the reasons you said, for the other reasons that people find these products potentially attractive and beneficial.

DR. McLELLAN: Barb?

DR. KOWALCYK: Barbara Kowalcyk. I wanted to follow up on something you said. You said that within the FDA -- and I don't know; maybe we will hear about this later -- you have already worked out the paradigm that you are going to be using for FDA-regulated

products.

Having worked kind of with both drugs and foods, there is a different regulatory paradigm depending on which type you have. Of course, with drugs, you have the precautionary principle. So the drug is assumed unsafe until proven safe. On foods, the hypothesis is very different. Food is assumed to be safe until proven unsafe. And since we are bringing this technology, as you said, from the drug side of things over to the food side of things, I wondered if you had given any consideration to the paradigm. So as a statistician, how you state the hypothesis is very important in driving how you look at a problem and assessing its efficacy or in this context safety.

So I was wondering. And maybe we are going to hear about this later in one of the presentations, but I was wondering, within the regulatory setting of FDA-regulated products, what paradigm are you planning to follow?

DR. GOTTLIEB: Yes. This is exactly the discussion we want to have. I think two things. One, the other products, like the fish, fall clearly within

our purview. So we have to figure that out.

I think what we know, what we understand, and what I meant to imply is we understand the science of cell culturing, you know, but what we don't understand is the yet -- or we haven't made decisions about because we are just getting this underway is what the policy construct is going to be. So we can understand the science of these processes. We can understand how these processes can go awry. We can understand how risk can be introduced in these processes.

But making the decisions around what we are going to require manufacturers to do to demonstrate, to make certain demonstrations as they implement their manufacturing processes, those are policy questions that we need to develop a framework around. That is exactly what we want to have a discussion around today. And that is exactly what we are currently grappling with.

We haven't made decisions around that. That is what we are going to be developing. So your point is very well-taken. All I meant to suggest is that I think we understand the science of the technology well,

the question of how we regulate it in this context. Those are regulatory and policy questions that we need to work through.

DR. McLELLAN: So, as you can see, Commissioner, as you step into some of these, we are actively engaged and happy to be a part of your discussion group. Thank you so much for giving us this time.

DR. GOTTLIEB: Thanks a lot.

DR. McLELLAN: We are here to serve the agency. So we appreciate it. All right.

Let’s go ahead and move forward. As most of you know, we operate by intensely diving in in many issues by subcommittee. We have one functioning subcommittee, with this guy right here. And we will be getting into that at a future time. But we did have one that got into the issue of NARMS, the National Antimicrobial Resistance Monitoring System. That subcommittee, of course, reported back to us, and we submitted that on to the FDA as a part of our review. That review was led by a number of members of this board.

And today we are going to be hearing response from the agency to that report, pleased to welcome back Patrick McDermott, who directs NARMS' program for FDA.

DR. McDERMOTT: Very good. Thank you.

COMMISSIONER'S UPDATE - SCOTT GOTTLIEB

RESPONSE TO THE SCIENCE BOARD'S NARMS REVIEW REPORT

DR. McDERMOTT: To Rear Admiral Hinton and to Dr. McLellan, to the members of the board, thank you very much for allowing me to be with you today to present to you our reply to a recent Science Board subcommittee of our National Antimicrobial Resistance Monitoring System.

My name is Dr. Patrick McDermott, and I am in CVM's Office of Research and director of NARMS. I know we are falling a little bit behind time. So I may touch lightly on most of the issues as best I can to keep us on schedule.

NARMS as a program is nested within our national strategy for combating antimicrobial-resistant bacteria, the so-called CARB program, where we emphasize five major goals, one of them being a strong national one health surveillance system. And within

that second goal, strengthening of NARMS is a priority of our national strategy along with enhanced collection and reporting of antimicrobial drugs sold and distributed for use in food-producing animals; more information on what is happening pre-harvest on the farm and the drug use environments; and then an injunction, if you will, to look across the spectrum of the food production chain to understand the dynamics of resistance in different ecosystems within and downstream of the drug use environment.

NARMS serves its purpose by monitoring trends in antibiotic resistance in the food chain, giving this information to people who can act on it to limit or reverse resistance. There is some element of research that is conducted to understand some of the gaps in the data. And ultimately it is designed if it is fit for purpose to help FDA in its regulatory decision-making to approve safe and effective drugs for animals.

NARMS performs this by -- and we have been at this since 1996. So it is a rich dataset in the program. We have a lot of experience in the processes. They essentially entail baseline data on the levels of

resistance in food animals that are derived meat products and zoonotic foodborne infections in human clinical cases, how resistance in those pathogens spreads from the use environment, the trends in data, whether resistance is improving or getting worse, where it might be coming from, how antimicrobial resistance is related to antimicrobial use, and then the burden of resistant infections in human cases of foodborne illness.

And then, with that information, to make decisions in cases where the trends need to be addressed to make interventions that might lead to a new baseline and a monitoring system that is working and will be able to detect the effect of those interventions.

The way we operate, NARMS is an interagency program. It involves working with USDA FSIS, who has nationally representative randomized sampling of national food animal production in the United States, which is quite an achievement, something that was instituted in mid 2013. And before that, we had relied on HACCP samples. It involves FDA's CVM's Office of

Research lab, which is testing the products corresponding to the four major food animal types and then CDC looking at human clinical cases, mainly salmonella and Campylobacter but other organisms as well. And then we combine these data. We generated it using harmonized methods and combined it into integrated national reports.

We have previously asked the Science Board to review NARMS or a subcommittee of the FDA Science Board to review NARMS in 2007. And we asked them to look at sampling, which really is the keystone of any good system, research studies and data harmonization reporting, and how we are working internationally. And we used that for our last strategic plan, which completed in 2016. It had four goals related to those four questions. And we completed 13 of the 14 objectives stated there. The one that is missing that is always a challenge is timely data reporting. It is difficult to get something like real time in a program as complex as NARMS, but we continue to work hard on that.

The new review conducted last year, again, we

asked the subcommittee to consider sampling as we moved towards One Health. So this is an important concept. NARMS has been described as an integrated surveillance system. The One Health framework of surveillance expands that, to include, well, the animal pathogens and the health of animals, environmental ecosystems, and the relationship of both to human health. And so in that paradigm, a different sampling scheme would be appropriate.

We also asked about what is the best way to publish and assess the relationships between annual antimicrobial sales data that we have at FDA and the resistance data, something that there aren't really defined best practices on. And then, number three, now that we do whole genome sequencing as a routine part of our surveillance, how would we report those data and describe trends in the resistome? This is an area of rapid transformation as affordable whole genome sequencing has become possible. And I will say a little bit more about that.

Here is the subcommittee. Dr. Nolan, who is on the phone, chaired the committee. Dr. Kowalcyk, who

is here and is of Ohio State University, was on the committee along with Lonnie King from the same institution; Lee Riley from Berkeley; Tom Shryock, formerly of Elanco; and then Mike Apley of Kansas State in their different roles as special government employees.

So what did they say, then, in response to these questions? I wanted to give a couple of just general comments that are very complimentary to the committee about the work that had been done, the progress that had been made, and the ability and the cooperation between the agencies. And I would like to say, following Dr. Hinton's comment about pride in our scientists, that this is an element of pride in this program. It really works well together between USDA, CDC, and FDA. And we valued that relationship very highly.

There are a lot of good synergies that come out of this beyond the original intents of the program into outbreak investigations and other food safety priorities.

They mentioned other ways in which NARMS has

been a model for other types of programs and including WHO's recommendations on how to build surveillance systems. I could add to that that the scientists in NARMS are members of the Transatlantic Task Force of Antimicrobial Resistance leading CODEX conversations right ongoing now about building integrated surveillance contributing to OIA's threshold cut a number of ways.

In addition to the questions, there was a call one day where the committee asked, "You know, your questions are good and relevant. Can we look beyond them, too, and give you just sort of an editorial of our own on how we think the program might be improved?" And so we are certainly eager to hear that. The thinking behind that was the opportunity that NARMS has to not just improve incrementally but to change transformatively within this One Health framework.

So in response to question 1, how might we improve our sampling, there are a few themes that developed throughout this that are consistent with the One Health description. And I didn't intend to put in here every question and answer, every bit of advice.

There were a lot of details that were administrative and so on. I wanted to touch on the ones that I thought were most important.

So one recommendation was to monitor pretreatment animal pathogen isolates from ill animals and those from treatment failures to understand animal health. And this theme of expanding beyond zoonotic foodborne to also look at pathogens in the animals is keeping with the One Health paradigm in a theme that repeats and one that we are eager to try and pursue. And this is a big challenge because it sometimes involves getting onto the farm or being in feedlots. In USDA, our partners in NARMS at USDA are really struggling hard to find ways to do this to ensure confidentiality and get the type of data that is actionable. And that language is also built also into the national plan I mentioned at the outset.

There was a recommendation to synchronize the HACCP and the cecal sampling; that is to say, the old and the new systems. That was an interesting idea. And we are looking for ways to overcome the logistics of that.

Environmental sampling of the production facility and waste stream and related sites. So this is a call for a new sample set. And it touches on the issue in One Health that is the environment. That is a big place, right? And there is no agreement on what type of environmental sampling would constitute best practices within the One Health context. One possibility is near the animal production facilities. Another possibility is effluent from hospitals. Another possibility is effluent from the producers of the active pharmaceutical ingredients. So there are a lot of points of exposure in surface water or treated water. So there is no agreement on it, but the conversations are going on about what type of environmental sampling is appropriate.

The fourth recommendation on sampling, add other commodities. You know, this is something we have wanted to do for a long time and one thing that was recommended, even in the review from 10 years ago. And so we have started pilots looking at seafood. This is mainly imported in the United States, but it is also an animal protein source that is produced with approved

antimicrobials and, therefore, I think within the remit of NARMS. And so we are looking at that, right now developing those protocols and anticipating looking at other animal products as well. So those are the highlights of the first question about sampling.

What is the best way to report on the relationship between sales and resistance data? The big concern here from the Science Board was that additional resources should be invested in investigating potential associations and actual use in resistance, rather than annual sales and distribution data, and concerns about that we might have detailed those data into too many categories already. And so we are going to continue to look for ways to do this well, but in the meantime, we are taking advantage of some opportunities to get good information on antibiotics and how they are actually used, rather than just the amount sold.

What is the best way to report the whole genome sequence data and trends in the resistome? This is a very large question. If you think about the complexity in the program before the age of genomics,

we were looking at salmonella. We look at salmonella, to take one example, from 12 different sources now in NARMS. And we compare that to human isolates. We look at resistance to 16 antibiotics. We look at serotype and historically pulse field gel patterns. Now we have piled on top of that three million nucleotides for every isolate. And now we have sequenced some 15,000 isolates.

So how do you make data like that digestible, if you will, to a broad stakeholder audience that has different levels of interest and understanding of it? We have invested in this because we were early adopters, if you will. And I am proud to say I think NARMS, along with our colleagues at CFSAN and CDC and USDA, have really pushed this technology farther and faster than other countries and farther and faster than it has been implemented for other pathogens. And so we have been doing some work on creative ways to show the data. One tool, resistome tracker, which essentially harvests all the genomic data from NIH every week, we do it right now. And we report all the resistance genes that are being found in salmonella, E. coli, and

Campylobacter. And we are providing that to whoever wants it. So it is an open system. It is as real-time as we can make it. And it is in fairly simple format so it will continue to try and improve.

The second recommendation with question 3 I thought was a very intriguing one: to report antimicrobial resistance trends by specific lineages that incorporates genotype and geographical data with visualization tools. This is a really creative recommendation because it acknowledges that we have moved beyond the old categories of characterizing microorganisms, which, say, may be serotype or even species, to phylogenetic lineages that might have selective advantages in certain environments or certain ecosystems or might carry with them traits that allow organisms to prefer the treatments in a plant that make them more prevalent in the food supply.

So we have gone from sort of two-dimensional datasets with genomics into a three-dimensional dataset, where we can see deeper into these sorts of traits and the associations that these traits have with different lineages. And now maybe we can report

resistance along those lines. I thought that was a really creative recommendation that we are eager to try and do. As CDC develops the whole genome MLST typing scheme to replace pulsed field gel electrophoresis and PulseNet, we will be able to start doing that.

And then the third recommendation, develop in silico serotype, strain-typing databases. This work has been ongoing for some time. You can infer serotype right from the genome. You can infer all sorts of traits. And we are working through an interagency group called GEN-FS, which is Genomics for Food Safety. And this is a working group of FDA, USDA, CDC, and NIH. And we are essentially coming up with all the categories of epidemiologically relevant traits to describe foodborne bacteria and with the intention of draping these datasets over isolates found in outbreaks or found through surveillance. So you can describe them in terms of, well, the lineages I just discussed, their whole genome MLST type, their resistance patterns. What virulence traits do they have? What salt tolerance might they have and all of the things you can infer from the sequence? So it will provide

for a very, very rich set, a rich vocabulary, if you will, of describing what we are seeing in our surveillance systems and the things that are allowing microorganisms to cause foodborne illness.

So beyond those, I am going to skim lightly through these last sections. So that was sort of the end of our recommendations on your specific questions, and then there were general recommendations based on this notion that NARMS really was poised to move in a brand new direction and not in incremental improvement. And so some of these are familiar themes, but the addition of environmental testing, which I described, is a conversation that is ongoing to try and define best practices and get data to help us understand where to begin.

Include food animal pathogens. We agree with that. And we think also companion animal pathogens should be part of it. There is an area of antimicrobial use that nobody has really tried to understand in terms of a One Health strategy. We think it is time to start looking at that and getting an idea of what risks might be associated with drug use in

companion animals.

And then there were some general recommendations about now that we have a national strategy to look for opportunities for synergies among other programs that have either emerged or been enhanced through that national strategy.

I mentioned getting on farm. That is a big challenge and something that the FDA is really working hard on.

Increasing collaborations, broadening collaborations. That is something we try to do as much as possible. Especially now with all of this genomic data and the shortage of bioinformatics specialists, we collaborate more and more with those with experience in machine learning and things of that nature, just to name one example.

Consider more in-depth and integrated collaboration globally. I think we are doing a very good job in that arena, but we certainly are always looking for opportunities to look to harmonize what we do so we can compare data. I mentioned the TATFAR as an example in WHO. We have also in NARMS started

inviting other countries to join our quarterly calls that used to be intramural. And so now Mexico is on our quarterly calls. Canada is, Chile soon going to join. We are going to try to get APEC countries participating so that we can move forward in a conversation that helps us all define best practices in different economies. So I think we do a good job in the international arena in helping others take advantage of our experiences and learning from theirs.

Number 7, envision how nerves might integrate with some micro biome studies. So this is essentially -- the micro biome can be described as the DNA constituents of a complex biological sample. So, instead of growing bacteria in the classical way and looking inside them and seeing what they have, you take all of the DNA out of a gemish, out of a food sample, out of intestinal contents, and you look for the microorganisms and their resistance genes in that DNA in total. We have been working a lot on this and have some really good work going on in that area. And some of it is being made necessary by market forces, which has made culture-independent diagnostic testing a real

challenge. We are not getting isolates for some bacteria because they aren't being cultured the old-fashioned way. So a lot of effort is going into this topic, and it is seen as really the next technological wave.

Then we were advised to take advantage of the recent approval of a new drug class. Avilamycin is attest case for emergents in spread of resistance. And we are definitely doing that.

And this I think really restates some of the things that I have said. In the interest of time, I might just skim over this, but it is more about exploiting genomics. And that is something we are doing with a lot of energy and making investments.

Dr. Gottlieb mentioned the recent release of the five-year plan for promoting stewardship in veterinary settings. And we have incorporated into this five-year plan the major elements in broader language that I just described to you. I don't think I will repeat them because we have gone over much of it, but I think the last -- this is online. So I think you can look and see how we have taken the recommendations

of the Science Board subcommittee and put them into this national strategy in terms of NARMS, in terms of getting new animal species and bacterial species and taking advantage of technology, and et cetera, and getting the use information, making it more valuable and working more broadly.

I want to finish by saying that we really appreciate the recommendations of the subcommittee of the Science Board on NARMS. It has been very helpful. It has helped stimulate our creativity energies. It has helped us think, really, about how we could improve in a transformative way in keeping with the One Health framework. And so we are eager to pursue the recommendations that I have set out as our priorities as best we can.

Now, many of them are aspirational. The majority of them are aspirational. And so they are dependent on new resources. And they are in our new five-year plan as things that are resource-dependent. And we will implement them as soon and as extensively as we can in ways that are commensurate with FTEs and resources to do the job.

So I think I got us back on time. So thank you for listening, and thank you for the invitation to be here today.

DR. McLELLAN: Thank you, Dr. McDermott. Very good. Appreciate your detail of your report.

Are there questions for Dr. McDermott? Annalisa?

MS. JENKINS: Annalisa Jenkins. Again, recognizing the remarkable efforts that have been made over such a sustainable period of time, I just wanted to pick up on, actually, a comment that you partially ended with, actually, as a segue into resources and new technologies. So it strikes me that enormous amounts of data and quantities of data across multiple dimensions, complex dimensions now, are in your hands as it relates to describing the current state of resistance and certain potential drivers and associations. So in the world now of AI and machine learning, could you just expand a little bit on your thinking around how to get access to the right capabilities and skill sets in that space to be able to align those because a lot of those, as we know, are now

emergingly increasing in the commercial sector, to enable you to perhaps drive your research in science and insights forward? Thank you.

DR. McDERMOTT: Yes. That is a very good question. And it points to a very large challenge, as you noted. I think everyone feels like they need more bioinformatics expertise in their institutions or companies or domains. FDA I think is in the same situation. We have invested in training our staff to learn the new technologies, in part, while at the same time, we have collaborated with experts in the field. And so we are trying. You know, we are trying to do the outreach and the collaboration, on the one hand. At the same time, we are trying to develop the in-house expertise.

But I guess one of the good things to anticipate is that many of it is becoming sort of pushbutton more and more. So, you know, we are looking in a very specific area of complex data that lends itself to pretty good automation. This was why we were working in this GEN-FS process to say let’s cure eight categories of traits that are important for different

purposes. Well, first, let's define them all, curate them all, and then right script on top of them to automatically put that information out. And that is what is going to happen at NCBI. So we have worked with them.

Now, they automatically predict resistance from the genomes. We have worked with them to develop that database. They automatically placed organisms on a phylogenetic tree. Soon they are going to automatically add the whole genome MLST to it. So all you have to do is look for those three things. As we continue to work, then it will automatically add all of the virulence factors that go with those organisms and, after that, all of the survival traits and so on.

So from the perspective of what we are doing in food safety surveillance, the GEN-FS process is going to help us meet that so that these things become automatic. But you are right. Going forward in many other areas of activity with big data, I think that expertise is going to be coveted, yes.

DR. McLELLAN: Lynn?

DR. GOLDMAN: Thank you. Truly, one, you

know, it was a very impressive review report. And then the response is even more impressive. And it is just great to see how FDA has really taken the recommendations to heart and is doing so much.

I wanted to make a comment, a small comment, really, about the environmental monitoring issue because it is something I am particularly interested in, but I saw that there were a lot of partnerships involved in that. And I am happy to see especially the engagement of the USDA. And I hope the CRS is in there. I was also thinking that it might be possible that FDA could leverage a little more from a couple of other agencies if there is away to work with them smoothly. And I am thinking about especially USGS and the EPA because they have a lot of expertise about how to go out there and take valid samples of water and dirt and all of that. I am an environmental health person. So we are kind of about dirt. Also, they are often out there doing it. And it is not expensive stuff, and it could be that they might be interested in piggybacking with you on some of that to just have a better understanding of what the baseline picture in

the world looks like.

I mean, one thing I am concerned about, if you are out there doing targeted sampling, what is your comparison? What is normal? What is normal out there because we have had a lot of antibiotic use for a very long period of time. And there are a lot of ways that these antibiotic-resistant pathogens can be moving around in the environment, including wild animals, birds, and so forth, spreading them. So I think it could be a really good idea to figure out if there is a way to do that.

And I am thinking about how FDA worked with EPA on the problem of the pharmaceuticals in the water. And USGS and EPA actually provided a lot of expertise suffer-free. And so, you know, it is just an idea.

DR. McDERMOTT: I can just say really quickly that we did invite EPA to our public NARMS meeting in October because they are doing surface-water sampling. And we have been in discussions with them about providing resources for doing the sequencing on those isolates. I think that that is a valuable dataset, and you are right that the wild animal migration is a known

vector of spreading antibiotic-resistant bacteria. And there is an elaborate theory on how salmonella thyphimurium DT104 spread around the world on migrating birds.

One of the advantages of the new genomics technology is it should allow us to look farther with the same resources, if you will, to some extent to start to explore what is normal in these other sample sets. And we don't really know that yet. I mean, we thought we knew it with phenotyping, but I don't think we can say with a lot of confidence we know what the normal background resistance level is in any of most animal species or ecological niches.

DR. GOLDMAN: One thing to just add, so the U.S. Geological Survey has done this brilliant work to track the migration of avian flu in wild birds. And I think this could be a very similar -- you know, they love doing that kind of thing.

DR. McDERMOTT: Yes. Thank you.

DR. McLELLAN: Yes? Go ahead, David.

MR. REJESKI: Yes. Dave Rejeski. I mean, the other option you have in terms of distributed

workforce would be citizen scientists. So, I mean, there are I think 1,600 groups in the U.S. that collect water-quality data. And a lot of those people have been trained up by EPA professionals and researchers. So these people are out there. I mean, obviously, there is actually an interagency working group of crowdsourcing and citizen science now. So most of the agencies actually engage a lot of people and train them up. This is happening. I am sure FDA is probably in the workgroup and USDA, USGS. So, I mean, this is an opportunity of using people that are naturally curious that want to do science, then have social impact. The question is, how do you get the proper distribution, the sampling, the QAQC? But there are certainly a lot of people out there that would probably jump on doing something on antibacterial resistance.

DR. McLELLAN: Any other questions? Anyone on the phone wish to question?

[No response.]

DR. McLELLAN: Dr. McDermott, we appreciate your report.

Ladies and gentlemen, we are ready I think

for a bit of a stretch and a break. So let's take 10 minutes, 15 minutes, and we will be back here for our follow-on.

[Break.]

MR. RAGHUWANSHI: If everyone could take their seats, we are going to go ahead and resume.

DR. McLELLAN: Okay. Welcome back, everyone. Glad to have you all returning for our follow-on session now on animal cell culture and food safety. Today, this is a very interesting topic on identification of possible hazards as well as nutritional considerations in the product of derived from animal cell culture technologies. As you can imagine, this is a hot topic. It is cutting-edge. And, as the commissioner noted, there is a lot of interest in this area.

I am very pleased to welcome the director of FDA's Center for Food Safety and Applied Nutrition. A good friend, Susan Mayne is here with us today. Dr. Mayne, thank you so much for joining us. This is an exciting area. And we appreciate you being here to give us a high-level introduction to the topic. The

floor is yours.

DR. MAYNE: All right. Thanks.

INTRODUCTION TO TOPICS FOR DISCUSSION

DR. MAYNE: Can you hear me? It sounds like it is working. Good. All right. Well, thank you, Dr. McLellan. Thank you for coming. Thank you for all the guests who are sharing your scientific knowledge, your expertise with us here at the Science Board here today.

We are at a critical juncture in this changing world. We at FDA stand ready to support the promise of animal cell culture and other emerging food technologies. We will always look at these advances through the lens of food safety. Innovative products must, first and foremost, be safe products.

As a regulatory agency, we know that sound policies are based on sound science. To ensure that Americans have access to the safest foods and that we have a strong program to address nutrition issues related to diet, we must base our decisions on the best available scientific information. Our ability to evaluate the safety of these products is rooted in science, in the knowledge we have about identifying and

preventing hazards. Our need to collaborate as scientists, to share data, and leverage resources is clear in this ever-changing global marketplace. We need validated practices and processes for safe production.

So the Science Board's input as the science advisers to FDA leadership is more important than ever. Your insights on how we can best protect and promote public health as we honor our commitment to advancing food technology is more important than ever. The breadth of the board's expertise, which includes food science, nutrition, toxicology, epidemiology, bioengineering, and genomics makes it uniquely suited to consider this complex issue.

So what is ahead for today? My role is to set the stage for what you will be hearing about from my colleagues in FDA Center for Food Safety and Applied Nutrition, FDA's Center for Biologics Evaluation and Research and from USDA's Food Safety and Inspection Service.

For a variety of reasons, applying animal cell culture technology to produce foods derived from

livestock, poultry, and seafood cells increasingly seems to be an idea whose time has come, but there are challenges that must be addressed, including considerations for food safety, throughout the culturing and harvesting of these biological materials and their further processing and packaging as foods.

We expect there are some lessons that can be drawn from previous experiences in various areas. These include known hazards and established best practices for production of traditional seafood as well as traditional meat and poultry production. We also may be able to gain some insights from the use of cultured animal cells for therapeutic applications, such as the development of vaccines, expression of recombinant proteins, and production of tissues and organs.

Are there any specific considerations we should bring to our safety assessment process for food ingredients when assessing the safety of materials used to culture cells or assemble tissues?

Finally, what range of nutritional properties might we expect from foods produced using cultured

animal cells? And how would these compare to the nutritional properties of foods produced by traditional methods from such animals as cattle, swine, poultry, and fish? How will the nutritional inputs into the cultured animal cell processes translate into nutritional outputs in final food products?

So, in closing, this kind of public science-based dialogue that we are having here today is critical if we want consumers to have confidence in the safety of the foods that are the fruit of these new technologies. Having food technology innovators engage with food safety experts and regulatory authorities is essential to building consumer confidence. Consumers care deeply about both safety and labeling surrounding their foods. And these are both roles that FDA has been charged with carrying out for the products that we regulate. We are looking at this technology as scientists and as regulators to help usher in a future in which innovation can help to ensure that there is plentiful food for everyone, food that is both safe and nutritious, because ultimately we are all consumers.

Thank you in advance for sharing your

scientific knowledge with us in this emerging area.

DR. McLELLAN: Susan, will you be able to stay with us for a while?

DR. MAYNE: I will be here for the whole day.

DR. McLELLAN: Wonderful. Thank you. In that case, we will hold on questions for a little bit later.

I would be remiss if we didn't allow Connie Weaver to introduce herself.

DR. WEAVER: So I was late because I was speaking at the FNCE meeting in town this morning about trust in transparency. And rigor and reproducibility items were all cared about.

I am from Purdue and happy to be here.

DR. McLELLAN: Thank you, Connie.

So we do have four presentations. We are going to be starting with Leah Stitz, who is with us from CFSAN. Leah is going to be giving us an overview of animal cell culture technology and provide a brief discussion, the key steps in the culture process at scale. So welcome, Leah.

We also next will then hear about the current

uses of cell culture and the concomitant challenges in clinical applications. And that will be coming from Cindy Osborn -- is that right? -- from the Center for Biologics Evaluation and Research.

And then next we are going to be hearing an overview of the food safety standards and typical considerations for both finished foods and food ingredients. So Jeremiah Fasano, thank you for joining us from CFSAN. And then, lastly, we will be hearing an overview of the hazards associated with traditional meat production and poultry production from U.S. Department of Agriculture from Emilio Esteban. Emilio, thank you for being here with us.

So why don't we start with Leah? If you would take the mike?

BACKGROUND INFORMATION ON

ANIMAL CELL CULTURE AND FOOD SAFETY

MS. STITZ: Good morning. And just a quick correction, it is Leah. And I am happy to be here. Thank you, Dr. McLellan, Rear Admiral Hinton, honored members of the Science Board, our special guests to the Science Board, and the guests in the audience.

Today I am providing you with an overview of animal cell culture technology for food production. First, we are going to define it for you. The definition that was put in the Federal Register notice is animal cell culture food technology, refers to the controlled growth of animal cells from livestock, poultry, fish, or other animals, their subsequent differentiation into different cell types, and their collection and processing into foods.

Here I have an overall schematic of the entire process from cell procurement and qualification, proliferation, differentiation, and harvesting.

Next we are going to review each phase a little more closely. First, there is tissue collection. You go to an animal. You take a biopsy. You place the collected tissue, typically muscle, in some type of solution, such as Hank’s balanced salts, to maintain physiological osmotic pressure and pH.

Next, you liberate the cells from the tissue. In muscle, which is what I am going to focus on for this presentation, you have to digest away the extracellular matrix in order to liberate the cells.

To do so, you can use classically derived or recombinantly produced enzymes. If one chooses to avoid the use of enzymes, there are other methods of cell liberation.

From these liberated cells, you select for myoblasts or satellite cells. These are uninucleate cells that capable of proliferating. And you now have a seed cell sample. This seed cell sample can possibly be used for the establishment of a master cell bank. Qualifying a master cell bank, usually 10 to 200 vials, involves quality control testing for the presence of viruses, bacteria, yeast, fungi, and mycoplasms, as well as cell line authentication.

We now take our vial of qualified cells. Currently there is a limit. We don’t have a whole lot of master cell banks available for the species that we eat meat from. So it will take a while before we have master cell banks for those, but we are at least qualifying those cells before going into the next stage.

Now we proliferate the cells. Basically, we are multiplying them. Cells require growth factors,

nutrients, gases, oxygen, and carbon dioxide to grow. Cell culture media is a solution that contains nutrients, growth factors, pH buffers, and other components necessary to grow cellular structures. Currently the primary cell culture media uses animal serum, specifically fetal bovine serum. Serum-free formulas for cell culture exist, but they are currently very expensive.

We have read that firms working in this space have a heavy focus on research to eliminate the use of animal serum and create economical serum-free media. Currently, sourcing, sterilizing, and certification requirements for cell culture media are designed for biomedicine. It is hoped by firms in the industry that requirements for cell culture media used for food production will be focused on food safety requirements, rather than biomedical requirements.

At this time, the technologies used for creation of food products from animal cell culture technology are on a laboratory scale. The cells being cultured in flasks are small bioreactors. To optimize cell attachment, plastic ware is either coded by the

manufacturer or if not, often by the end user for cell attachment. Choices include collagen, fibronectin, laminin, gelatin, and other cellular matrix components.

Bioreactors for proliferation do not necessarily require cell attachment. Instead, the cells are proliferated in suspension. Those bioreactors will likely be stirred tank reactors, which are already developed and currently in use for things like vaccines.

Next, we move to the differentiation phase. We still need the nutrients. We still need the gases. We still need the growth and biological differentiation factors. The growth factors now are specifically selected for their role in differentiation of the cells. For most structured food product applications, scaffolding is required in order to grow the cells and have them adhere to each other in any sort of 3D manner.

Scaffolding and structural elements are other areas of research and innovation. And going forward, we may see both animal- and plant-derived scaffolding used for these products. We anticipate that

scaffolding may be developed using 3D cell printing, recombinant microbes, hydrogels, or yet-undiscovered structural elements. Because the scaffolding may be consumed as part of the product, depending on its function, perhaps as a bone, which likely wouldn't be eaten, or connective tissue, which could be eaten, it really should be edible, low-cost, and its components must be readily available.

To achieve a food product that is comparable to conventional meat, different types of cells could be co-cultured and/or differentiated in a 3D scaffolding structure. The scaffolding must allow nutrient media to profuse the structure such that all cells continue to receive the nutrient media.

The next phase is harvesting. The biological material, whether it be clumps of cells, tissues, or tissue-type products, will be harvested. Once the material is harvested and is no longer supported by its life-sustaining culture media, the cells will soon become nonviable. Following harvest, the material then enters the traditional food-manufacturing, -packaging, and -labeling processes.

And this concludes my presentation. Thank you.

DR. McLELLAN: Any questions? Scott?

DR. STEELE: Thank you. Scott Steele, University of Rochester.

You mentioned that the master cell banks are qualified. Are there existing standards for that or who is qualifying them?

MS. STITZ: Currently the cell media -- there is FDA guidance for the qualification of cells and cell banks for biomedicine. That would probably need to be looked at and evaluated for its application to cells for food production.

DR. STEELE: That hasn’t been done at this stage, though?

MS. STITZ: No.

DR. STEELE: You were just saying you could model from that? Thank you

DR. McLELLAN: Sean?

DR. XIE: It is a very nice overview. Sean Xie from University of Pittsburgh School of Pharmacy. So the question number 1 is produce the cell culture

foods. What is the key difference with produce cell culture drug, biologics?

So the second thing is you mentioned about you are going to add a lot of growth factors. That is including cytokine hormone at harvest stage. My lab does protein expression purification using bacteria, virus, and E. coli. So at the last stage, you want to study to get the purified protein. We have to go through a lot of processes. Assuming in harvest stage, you are going to go through a larger-scale purification to remove those growth factors. Right? Because the residual hormones and also cytokine could be things getting to bother with causing a side effect like antibody-related.

MS. STITZ: I actually consider those processes to be, those purification processes to be, part of the harvesting process myself --

DR. XIE: Yes. Yes.

MS. STITZ: -- and anticipate that those would be done by the firms producing the products. One of the things that I meant to mention in my presentation is that each of these phases potentially

could be handled by different companies, companies specializing in each different segment. You could have companies going from the beginning of the process of, you know, procuring the cells, creating cell banks, and qualifying the cells all the way through to harvest, and further processing or each different segment phase could be handled by a firm, then leading to another -- that firm purchasing that product, and then continuing the process from that point. So we really have to consider those transitions and whose responsibilities begin and end at each one and how we make certain that the supplier has met the requirements for the following phase.

MR. FASANO: If I could just add, in terms of the residual media components and potential impact on safety, that is actually one of the questions we will be asking you about a little bit later. That is definitely a pertinent one.

DR. McLELLAN: Okay. I have got Cindy, Dave, Tony, Lynn, and Annalisa, so in that order. Cindy?

DR. AFSHARI: Yes. Thank you. Cindy Afshari.

I just had a question. And thank you for the overview. It was really, really clear and very helpful.

You mentioned -- and it may have been Sean's question -- that when you think about maybe the production of recombinant biologics right now, which happens through large bioreactors, that you envision the scale being different for foods produced potentially in bioreactors. And I was just wondering what you are thinking in terms of the magnitude difference of scale there.

MS. STITZ: I believe it is in order to create a kilogram of meat product, cells to do a kilogram of meat product, takes a -- I am trying to remember -- 500-liter bioreactor. I am not positive about that number. I need to look at my notes. Please let me get back to you on that for sure, but it is a significantly larger scale required. The exact scale, I need to double-check my notes.

DR. McLELLAN: Dave?

MR. REJESKI: I realize we are at a lab scale now, but I was trying to get a sense of production

synergies in the waste stream coming out. So will the process generate waste? Is it a biohazard? Would EPA see it as a hazardous waste? Is it compostable? Could I use the waste as an input to another process? If I have to use CO2 going into this, could I grab it from a power plant? I am trying to get a sense of kind of the, sort of the, transition zone between the processes and sort of the outside world, just on the waste end, and then also inputs.

MS. STITZ: Currently, the firms working in the area are also looking at as much as possible reclaiming and reconditioning the cell culture media to use again. So they really are looking at limiting the amount of waste produced as much as possible.

MR. REJESKI: So it is a closed system?

MS. STITZ: As much as possible.

DR. McLELLAN: Okay. I am going to ask each of you, pull your microphones a little bit closer because we are having a hard time hearing everyone.

So let’s go to Tony.

DR. BAHINSKI: Hi. Anthony Bahinski. So the process you outlined, you really focused more on

isolating endogenous cells to develop your master cell banks. What about other methodologies, such as genetic manipulation or chemical modulation, to generate a proliferative cell, so you could increase the diversity of potential animals or species that you could probably bring into that?

MS. STITZ: At this time, the firms working in this space are avoiding genetic engineering, bioengineering of the cells because they don't want their new cultured meat products connected with biotechnology. In the future, once the product is accepted by the consumer, they might be willing to consider that pathway, but currently the firms working in this space are trying to keep a very clear separation between we are taking cells from a live animal, the animal is not being harmed, a lot of what is driving this is the current industrial agricultural model and people not being happy or satisfied with the suffering of the animals. So the people working in this space really don't want to get into genetically engineered, at least not at this time. It could happen, and it is something we should consider.

DR. BAHINSKI: Sure.

MS. STITZ: You know, another thing that has been brought up in some of the ethics papers on the topic is what is to keep somebody from growing human meat.

DR. BAHINSKI: I didn't want to bring up the Soylent Green reference, but, you know, that --

[Laughter.]

MR. FASANO: I think, just to add to that, I will say there is a lot of interest in trying to introduce more plasticity into the cells that you recover to differentiate them into a variety of cell types. It is definitely an active area of research, both in this and in a number of other technical areas.

DR. BAHINSKI: Yes. But, you know, in the spaces of IPS cells, you know, they are moving beyond just genetic modification. You know, there are chemical ways to modify potentially even waste. You know, the mechanical substrate which the cells are grown on could differentiate. But I understand. Thank you. That is very informative. Thanks.

MS. STITZ: Thank you.

DR. McLELLAN: Lynn?

DR. GOLDMAN: Thank you.

I, similarly, actually, to my next-door neighbor here, was very interested in the issue of, you know, what does it really take to make a kilogram of this kind of meat, even though understanding it is still very experimental? But we do have a pretty good sense with, you know, when we make meat using cows, what kind of carbohydrate intake they need to have, the efficiency of conversion, of the energy intake, from what they consume to, what ends up in meat, the protein as well, the efficiency of that, how much water you use, the energy that you use.

And I guess, you know, before reading the background material for this, I really hadn't given much thought to the fact that, actually, you know, there is a substantial amount of input of energy and water as well as nutrients into this process. And so I was just trying to get a sense quantitatively in terms of, you know, if you have -- not only how big is a bioreactor, but if you are trying to produce a kilogram, like how much bovine fetal serum do you need

and how much energy input in the way of carbohydrates, energy per se, water? You know, what actually has to go into the system in order to produce a kilogram of meat this way if people have a sense of that?

MS. STITZ: From one of the papers in your background reading, applications demonstrate expansion in bioreactors up to 5 liters, but with currently commercially available technologies, there is a potential for bioreactors up to 2,000 liters. To put into context the scale of cultured meat production in the region of 8 by 10 12 cells are required to acquire 1 kilogram of protein for muscle cells, which would need a traditional stirred tank bioreactor in the order of 5,000 liters. So I was off by a factor of 10.

DR. GOLDMAN: Are there references in -- I didn't read all of the citations to that, but is there more reading that we could do to learn a little bit more? So what is the input in that tank, you know, in terms of how much carbohydrate, essential amino acids, bovine fetal serum do you have to put in there to generate that kind of production of cells? It seems like a lot of cells, but it doesn't look like it when

you just look at a kilo of meat.

MS. STITZ: True enough. Personally I have not double-checked the referred article by Schnitzer, et al., 2016. I don't believe that that article has the information you are seeking, though. I am not aware of the publication that has that information.

DR. MAYNE: But, Lynn, maybe I can add one thing. Some of the reading that I have seen in this area in a traditional setting, a lot of those inputs are going to form things like bone and brain and things like that that are not transformed into edible product. So in this setting, the efficiency in terms of the amount of edible product that is achieved out of that is very different than in the traditional setting. I don't know if that helps.

DR. GOLDMAN: I am not sure myself either, Susan, because I know that the cells in culture don't gobble up everything in their culture medium, right? They are not 100 percent efficient. I know that from other areas that I have been involved with. So you have to have a certain amount of a nutrient to make it available to the cells. And so, you know, I think it

would be something to learn about over time because I think that some of the issues around what is happening, well, environmentally, what kind of waste is there, what kind of energy consumption is there are somehow connected to that as well as, you know, what do you really need -- and back to the other question, what do you really need to be adding in the way of hormones and growth factors and so forth to make the cells differentiate growth the way you want them to?

DR. McLELLAN: Okay. I have got Annalisa, Lisa, Connie, Rodney, and Barb. So we have quite a bit. We will try and keep it moving along. Okay? So Annalisa?

MS. JENKINS: I just have a couple of comments, really, to add to the discussion. Yes. So the first comment relates, actually, to the fetal bovine serum topic. So, as you know, my background is in pharmaceutical R&D. And so I have extensive experience of the challenges that we have faced in the last 10 to 20 years with the acquisition of a stable, predictable quality supply, the fetal bovine serum. I am reflecting on the time when Merck/Serono struggled

extensively to continue a supply of Rebif for multiple sclerosis into the U.S. market because there were so few suppliers of high-quality fetal bovine serum in certain amounts. So I just would like to add just a comment to the record that whilst this is at laboratory scale, clearly if this is going to be required in the context of this process, I believe it is going to provide quite a challenge. So that is my first comment and also a challenge in that a lot of this comes from outside the U.S., as you know, from other parts of the world.

The second comment relates to a scaling and building on previous comments. We know from our work in cellular therapies that whilst we are in roller bottles and it is small-scale, we can look at the key quality attributes, safety parameters, assays for final release. But what we really know is that we need to be scaling to 50 liters, 100 liters, and up to the thousands to really truly start to understand what are the potential issues, the key quality attributes that will ensure a sustainable, predictable supply of the products.

And so, again, I would just like to add commentary to the record that whilst we are really at laboratory scale today, I believe that a number of the challenges in manufacturing at scale are largely unknowable and, therefore, will need to be the result of scientific study.

Thank you.

DR. HURSH: Excuse me. Could you all please speak up?

DR. McLELLAN: Yes.

DR. HURSH: We can't hear you.

DR. McLELLAN: Just a minute. So I just was going to ask everybody, grab those microphones. Pull the cords. Pull the whole thing closer to you because we are not hearing the commentary, and it is essential that in a public meeting like this that we do that.

Response back?

DR. MAYNE: Well, I was going to say one thing. There were so many questions here. I just wanted to let folks know that we do have a couple of more overview presentations. And I am wondering if we should jump into those first and then get into the

questions this afternoon because we have several more introductory presentations that may help to at least shed a little light on some of the questions everyone asked.

DR. McLELLAN: I have one question on the phone, though. And so I will end with Lisa, and then we will move on if that is okay, folks. Go ahead, Lisa.

DR. NOLAN: Thank you.

I really appreciated the overview as well. One thing, when you were talking about the qualification of the sales, I wondered about prions. How will you ensure they are not in the sales that are selected?

MS. STITZ: I don’t know exactly how that process works, but I do know that it is addressed in the FDA guidance.

DR. NOLAN: Thank you.

MS. STITZ: Thank you.

DR. McLELLAN: Okay. Let’s go ahead and move with Cindy and your presentation. Thank you.

DR. OSBORN: All right. It is a pleasure to

be here today and share with you my talk on the current uses of cell culture in these challenges in clinical applications.

Office of Tissue and Advanced Therapies and Center for Biologics Evaluation and Research regulate OTAT products which include gene therapy, tumor vaccines, stellar immunotherapy, stem cells, xenotransplantation, human tissues for transplantation, bioengineered tissue, and certain medical devices. And this talk will be from the perspective of our experience with cell culture in therapeutics.

So as an overview of the current uses of cell culture in clinical application, we use cells as a source of production of recombinant proteins, virus, vaccines. And this can be animal or human cells. It can be primary or immortalized cells. It can be diploid or aneuploidy cells or tumor-derived cells. Although pharmaceutical industry has been producing recombinant proteins for a long time, cell has been used as a means to produce a protein product. So although a lot of general knowledge is known to use cells as factories, there are a lot of additional

considerations when cells are actually the product.

Our real experience of this comes from using cells as therapies. And these can autologous or allogeneic cells. It also comes from cells that are genetically modified and cells that are grown in materials or scaffold.

So when we think of challenges to cell culture in clinical application, we think of the whole process. We start from the beginning of things that we put into the process and the kind of contamination that we can see source contamination. We also look at the manufacturing process itself in process contamination that can happen and the output, which is the purity of the product. And there is an additional challenge when you are growing cells in the materials or scaffold. And, of course, after you figure all of this early development, you actually earn the path process of scale-up, which has been brought up before.

So I am going to start with the first challenge, which is source contamination. This can come from cells and the reagents. Examples of this are viruses, mycoplasma, bacteria, and fungi. There are

approaches to address these challenges. For the cells part, you can actually test the donors of the cells or tissue materials. In the case of animal cells, you can test for animal-specific viruses. And for things that you cannot test, you can actually control the source by having, for example, samples taken from close herds, where you can have the history and the infection status of the animal that you derived this from.

In the case of cells that are derived from banks, you can actually test the starting cells or the tissues. And for whatever that is missed during this testing, you can actually extensively test the cell bank in the later stage.

In terms of the reagents, you can actually qualify the reagents based on the information from the supplier. Otherwise, you can actually test the reagents yourself. And for whatever you don’t catch, you can actually test the cell bank as well in the end.

I am going to move on to in-process contamination that can come from the operator, the manufacturing equipment, or the reagents. An example of this is the chemicals, toxins, adventitious agents,

allergens, or leachables. I wanted to emphasize that comparative regular food-processing plant contamination in cell culture is extremely easy to do if you are not careful because the culture condition required to grow cells is very great for growing bacteria and mold as well. So contamination can rapidly expand and spread.

So approaches to address contamination introduced by the -- I'm sorry. In order to address this in-process contamination, there are a couple of strategies. In terms of controlling for in-process contamination introduced by the operators, you can use aseptic techniques. This is a very important concept. In the case of OTAT product, we don't normally have the option of terminal sterilization. However, in the case of product which can possibly be terminally sterilized, you still want to make sure that the manufacturing process is done aseptically to decrease the potential of bioburden introduced by bacteria coming either from the input or from the manufacturing process, which, even after a terminal sterilization, the bacteria can still introduce endotoxins through the product.

Additionally, you can address in-process

contamination because of operators using closed systems or automation. So traditional cell culture is very expensive because there is a lot of hands-on work. It can be more economically viable to have highly automated facilities and robotic workstations that can run 24/7.

In terms of addressing in-process contamination due to manufacturing equipment and reagents, you can introduce single-use system, such as the use of disposable plastic bioreactor and tubings. You can also perform reagent qualifications, such as using serum-free media, which was brought up before, and antibiotic-free media. You can also perform process controls, such as specific lot release, to demonstrate safety, which can include testing for levels of residual toxic components.

Another point I want to bring up is advanced manufacturing; for example, 3D printing, which at this point is still very aspirational technology, but it can be revolutionary in terms of the flexibility when introduced to the process.

In terms of frequency of in-process

contamination, based off of our experience, this really is commensurate with the training and experience of the manufacturer itself.

Next, I am going to talk about the output, purity of the final product. This is basically looking for presence of undesired cell type in the final product. Example of this can be undifferentiated cells or misdifferentiated cells. It can also be residual cells from incomplete selection process or residual materials from cell culture that can be toxic, allergenic, or inflammatory. Example, it can come from biologics; for example, the cytokine or growth factor that went into the manufacturing process. It can also be from the residual small molecule from the manufacturing process, not just antibiotics.

The approach to address this challenge is by performing product characterization. The majority of differentiation protocol is never 100 percent. And part of the manufacturing process control will be to demonstrate consistency in terms of identity and proportion, the ability to manufacture desired cells with a minimal number of non-desired cells.

Another approach is to test for any residual small molecules that can potentially be allogenetic or toxic in the final product.

Next, I am going to talk about challenges that we have seen when cells are grown in materials. So in OTAT, in the therapeutic context, we have seen very varying types of materials and scaffolding. We have seen natural polymers, such as allogeneic Matrigel, collagen, and laminin. We also have seen synthetic polymers, such as PLLA and pGA. And we also have seen really hard material, such as ceramics.

The main challenge when growing cells on materials is assessing how the cells interact with materials. And there is a certain approach to address this. It can be through the characterization of the cell scaffold products. It can be by testing the biocompatibility of the material, such as to support the safety of the scaffold and looking at the degradation kinetics and the degradation of the byproducts for its identity or toxicity.

Next, another challenge that we commonly see is the manufacture process scale-up. We commonly see

problems due to changes in cell density in sheer force, dissolve oxygen and nutrition conditions, which are not scalable linearly and have profound effects on cell behavior, such as growth rate of the cells and accumulation of delayed trace genetic mutations of the cells.

Often, scale-up requires adherence culture to change or adapt to encourage independent suspension culture condition. This changeover from attached cell suspension can affect the characteristics and features of the final cellular product. For example, you can see a significant change in distribution of wanted versus the unwanted cells.

The last but related important problems with scale-up manufacture is the raw material supply, which has been brought up previously. It is often hard to source large enough supply of reagents during the scale-up process. For example, if you are scaling up from 1 liter to a 10,000-liter bioreactor, it can be a challenge if you are using a growth factor that is manufactured by one company in the world.

To overcome these issues related to scale-up

and the implementation of the manufacturing process change, some manufacturers decide to, instead of scaling up, scale out. What this means is that, instead of increasing the size of the bioreactors, they decide to keep the small bioreactor but to have more of them. However, to be fair, this is not without its problem because more reactor means that you need more space. So there is definitely more cost, and you need to have more space. So it is not the ideal situation for some manufacturers.

The last concept I want to introduce is risk-based control. This starts with the identification of the potential risk. And it can be in identifying process-related vulnerabilities, such as maintaining sterility in filling procedures. And once the potential risks have been identified, process control can be used to assure the quality of the product. This can involve deciding manufacturing process that negates the potential vulnerabilities in testing for these potential failures. Once designed, inspection and record implementation procedures will ensure compliance and quality control.

I wanted to end by saying that manufacturing technology is still evolving. The field is so new and exciting. It remains to be determined exactly how commercial scale production can be accomplished. However, it is important to keep an open mind and take into account a lot of scientific engineering and regulatory consideration to deliver the safest products to the customer. Thank you.

DR. McLELLAN: Thank you, Dr. Osborn.

We will allow questions directly to Dr. Osborn's specific comments. If it is more general, let's save those until the end. Are there any questions for her? Go ahead, Dave.

MR. REJESKI: I was just trying to get a sense of when you were describing what is in existence now, is this batch process or is it actually continuous 24/7, it is just running constantly? Because that has a huge impact on how you scale, although small batches actually is something that continuously runs.

DR. OSBORN: Okay. So I just wanted to clarify your question. Your question is whether currently what we are seeing is batch manufacturing --

MR. REJESKI: Right.

DR. OSBORN: -- versus continuous manufacturing. We actually see mostly batch manufacturing.

MR. REJESKI: Batch. Okay. All right.

DR. McLELLAN: Rhondee? Go ahead.

DR. BALDI: I just had a question about the independent suspension culture. And you said it changes the characteristics for features. Do we know how it changes the characteristics for features of the final product in terms of --

DR. OSBORN: So you are asking if --

MR. RAGHUWANSHI: Could you please repeat your question real quick a little louder?

DR. BALDI: Sure. Sorry. Yep. So you mentioned that in the independent suspension culture, that that may influence the characteristics and features of the final product. And I wondered if we know about the range of those characteristics, the changes that occur. Do we know or we don't really know?

DR. OSBORN: The short answer is probably no

unless my -- yes, the short is no.

DR. BALDI: Okay. So we don't know if it is --

DR. OSBORN: It really depends on, you know, the kind of cells you are growing. It really depends on how much you are scaling up and how you are scaling up.

DR. BALDI: So for muscle cells particularly, we don't know if it changes nutrition. We don't know what it changes exactly.

DR. OSBORN: I personally am not an expert on muscle cells growing in bioreactor.

DR. BALDI: Okay.

DR. McLELLAN: Well, I have two more over there. And then we will --

DR. SHEETS: Okay. I wanted to specifically address her question.

DR. McLELLAN: All right. Go ahead.

DR. SHEETS: May I? So cells that grow as adherence cells have a lot of extracellular -- and extracellular matrix that allows them to adhere to a surface. And there are a lot of proteins and so forth

that are involved in that. When you grow in suspension, a lot of that is, you know, allowing the cells to grow in the absence of that sort of matrix and to grow without contacting cells next to them. So there is a lot of changes in gene expression and in what proteins and other factors are being produced and being used by the cell for growth. So there are a lot of changes that are caused by growth, adaptation to growth and suspension. Does that help?

DR. BALDI: That does help.

DR. McLELLAN: Annalisa? No? Okay. Sean?

DR. XIE: Very nice talk. And I --

DR. McLELLAN: Sean, you need to pull your microphone to you, please.

DR. XIE: Very nice presentation. So what I try to ask is a little bit technical. You mentioned the undifferentiated cell and the misdifferentiated cell. So in many cases, you grow the cell culture, you get unwanted material. How do you control those growths in the technical part?

DR. OSBORN: I am going to try to answer. And my management can try to add stuff. But I think we

just test for those. You know, doing your culturization in early development, you will test for those cells that you don't want. And as you go through, you just want to make sure you are consistent and you have demonstrated that those cells are safe in some sort of -- for us. For therapeutic, it will be preclinical data.

DR. XIE: Okay. Thank you.

DR. McLELLAN: Okay. We have the last question. Barbara?

DR. KOWALCYK: So I had a question. I have heard a lot in your talk about testing as a way to ensure that the product is safe. And, of course, sampling is a challenge. Do you have any sense of, you know, if these are rare events, you -- just to go to the point of misdifferentiation, if these are rare events, you have to take a lot of samples, sample a lot of cells to even find them. But I don't really have an understanding of what the testing process is. Could you please elaborate on that? Is it a destructive process? How difficult is it to do? Because this is an important point if we are going to rely on testing

as a way to ensure the safety of these products.

DR. OSBORN: So, if I may clarify your question, are you asking how much sample is needed for the testing and whether it is destructive?

DR. KOWALCYK: I am just asking about the testing process to find these misdifferentiated cells or the contaminants. What is the test? And how is that performed? Because just from my knowledge in food safety, we have contaminants that are not heterogeneously distributed in the product. And when they occur at low levels, you actually have to increase your sample size in order to be able to find them. I am just trying to get a sense as to what the testing process is.

DR. OSBORN: I am going to try to answer. So I think it depends. It really depends on the data you present to us and how good your process control is if you can keep those -- during the early development, when we were testing them, if you can keep showing us consistency in terms of how much percentage and the identity that you are seeing. So if you have a good handle, I believe that, you know, by performing a lot

of the preclinical studies, you just test. Like there is a guidance for sampling as well that I believe the sponsor has to -- the manufacturer has to follow.

MR. RAGHUWANSHI: If there is someone from CBER?

UNIDENTIFIED SPEAKER: Yes, I am here.

MR. RAGHUWANSHI: You can either go to the mike at that table or you can feel free to step up to the aisle mike if you want to clarify an answer.

DR. KOWALCYK: If I may, just a minute? This goes to my earlier point this morning in that your sampling strategy does depend on your hypothesis. And, you know, if your hypothesis is the product is safe until proven unsafe, you can effectively achieve that by underpowering your study.

DR. OSBORN: I believe that would not be our hypothesis.

DR. KOWALCYK: But in food, that is. In drugs, it is not. So it is an important point for us to consider which paradigm will these products fall under.

UNIDENTIFIED SPEAKER: And I would agree that

is a very good point. It is not clear in a food product that misdifferentiated cells would be as big a concern because you would be consuming them, as opposed to implanting them in a patient. So I think it is a fundamentally different question, but I think the point Dr. Osborn was making us the testing is destructive. You know, we look for genome testing. We look for cell surface markers. We are interrogating a sample from the culture. And it is definitely destructive.

But in the early stages of this, we establish that you can make a product consistently of a certain purity. And then we can kind of step back a little bit on how much testing. And we do appreciate you cannot continually test because of the sampling problem. There is a power issue, but then there is a you won't have anything left issue. And so I think in food, this will be a fundamentally different question.

DR. McLELLAN: Thank you, Dr. Osborn. Appreciate your presentation.

Why don't we move to Dr. Fasano and our discussion of typical standards?

MR. FASANO: Okay. Thank you.

So you have already heard a little bit about the underlying technology and about some of the applications in the therapeutic space. Now I am going to provide another piece of the puzzle that hopefully will be of use for you in your deliberations later today. And for some of you, you may already know this. I apologize in advance. Hopefully for some of you, this will be useful.

I am going to talk about some of the criteria we use for evaluating food safety, some of the sort of tools and processes, and some sort of historical experiences with innovative methods of production for foods that may be tangentially relevant or provide some information about how we would approach a new production technology.

Let’s get some of the less exciting stuff out of the way first: foods. The Federal Food, Drug and Cosmetic Act defined it as anything used for food or drink by man or other animals. That also includes any articles that are components of those foods. So things that go into foods are also foods. And then there is also chewing gum, but we are not going to talk about

that today.

So the act also lays out some critical requirements in terms of safety and the way these are expressed as things that adulterate food, things that make it unsafe and, therefore, unlawful. So these are essentially things you are prohibited from doing. Food can't bare or contain a poisonous or deleterious substance that may be injurious to health, but the act does differentiate between things that are being added to the food and things that are sort of naturally present or are existing constituents of a food. If it is an existing constituents of a food that is naturally present, then the sort of prohibition is unless it is present at a level that is not ordinarily injurious to health.

So an easy way to conceptualize this is to think about, say, plants. They make a wide variety of secondary metabolites. Those secondary metabolites, many of them, are designed to repel herbivory, animals, insects, fungi trying to consume the plants. And so for some of those at some level of consumption, they could be problematic for humans. And, in fact, in some

wild varieties, that is the case that these are, some of these metabolites are, present at levels that would be of concern. But in modern agricultural varieties, these substances, while they are detectable, are not present at levels that would prevent any plausible safety concerns. So that is a nice illustration of thinking about the quantity of this substance not being ordinarily injurious. That is a standard for constituents that are present.

Two other key provisions relate to food additives and in sanitary conditions. So we will talk a little bit more about food additives in a bit, but essentially if a food additive is unsafe, what that means here is it either hasn't been approved by FDA prior to use or it doesn't fall into one of the categories of exemption from that requirement for approval. If it doesn't meet either of those conditions, it is an unsafe food additive, it adulterates the food, it can't be in food.

The other piece of this is in sanitary conditions. I mean, this essentially goes to microbial contamination if you are preparing, packing, or holding

food under unsanitary conditions where it could become contaminated or rendered injurious to health. That is also prohibited. There are other adulteration provisions, but I think these are the most relevant ones today. So we will stick with those.

FDA's approach to food safety emphasizes preventive controls. An effective prevention control is one that is informed by a hazard analysis of the specific food facility and then matched to the risks that are identified in that analysis. This sort of systematic hazard analysis and preventive control identification approach is very useful considering the wide variety of foods and facilities that FDA is involved with.

This sort of process was developed in a number of specific food areas early on; for example, seafood, but, in fact, you have heard mention of FSMA earlier today. Now, by law, all food facilities are required to have a food safety plan that includes a number of specific elements listed, some of them here. There is the hazard analysis itself. Any known or reasonably foreseeable hazards need to be included.

They could be biological, chemical, physical. You need to identify appropriate preventive controls. They could be a variety of different types. You need to have oversight and management of those controls so if the controls are not effective, you can detect that, correct it, and verify the correction. If your hazard analysis identifies risks in the supply chain, you also have to address those in your food safety plan. All of this needs to be documented and available for inspection by FDA. So that is a sort of a key tool, this food safety plan, in identifying specific risks for a facility and managing them appropriately.

So, having talked a little bit about food manufacturing, let’s now talk about food ingredients. I have put a definition up here. This is extremely broad. Any substance the intended use of which results in its becoming a component of food, may reasonably be expected to result in its becoming a component of food, or in otherwise affecting the characteristics of food. That is a lot of stuff. You can see in that last level there, including any substance used in producing manufacturing, packing, processing, transporting, so

forth. So it is true that, as a practical matter, many of the substances that are in that sort of last box may not have any meaningful effect on the characteristics of the food, but as a starting analysis for food safety assessment, the field is very broad.

So you have already heard me talk about the safety standard for substances that are components of food naturally occurring. The safety standard for substances that you add to food as food ingredients is reasonably certainty in the minds of component scientists that no harm will result from the use under the intended conditions. Right? So this is not an absolute safety standard. It is reasonably certainty by qualified scientists that no harm will result from the intended use. A number of factors go into that. There is the identity of the substance, exposure to that substance and related substance, potential metabolites produced after consumption, appropriate data and information for the substance, and then appropriate safety factors. And to talk a little bit more about how we sort of make that operational, I mean, identity and exposure are a critical starting

point. Depending on what the exposure is to a substance, that is going to have a huge impact on the kind of information that you need to determine whether the use is safe. At very low exposure levels, a substance might not present any problems, but at, you know, three or four orders of magnitude higher potentially could be a concern. So that will drive a lot of the questions you ask.

In terms of identity, this is an interesting one because there is actually an increasing number of tools available that will allow you to infer information about the properties of a substance from identity of that substance or related substances through things like quantitative structure activity relationships, other kinds of read-across data, various kinds of pharmacokinetic modeling, even information about potential ligands. A substance might interact within the body. So this is all information that could drive your determination of what information you need to make a safety assessment. What additional data would be appropriate?

Just to take one extreme example, if you are

looking at a protein from a potentially allergenic source as an ingredient, you obviously have concerns that are specific to induction of allogenetic responses into susceptible individuals, but traditional tox endpoints are not really going to be meaningful for a protein from a food source. So you really have to sort of match your endpoints of interest to the properties of the substance.

I am just going to finish up by talking about a few different examples of classes of substances that we have looked at in the foods program that are produced through sort of innovative biologically based processes. So the first one is substances produced by cultured cells.

This actually has a very long lineage. It started with enzymes secreted by fungi into cultured medium that were used for various food technology purposes. We have certainly seen those. But many recombinant proteins are produced for use as food ingredients by microbes, by fungi. We have seen oils produced by cultured algae. And so there is a wide variety of substances that are often recombinant

proteins but some other complex fermentates that are produced from a cell culture process. When we look at those, in addition to the properties of the substance itself, which, of course, is always a key point of focus, in terms of the manufacturing, we are also thinking about, you know, potential unwanted metabolites or expression products and then, you know, any potential contamination of the process by other microbes.

In addition to using the cells as production platforms, we have also seen cultured cells generated as direct food ingredients. Yogurt is the most everyday example here. You think about, you know, yogurt having bacteria in it. But we have seen in the foods program a number of microbes grown up in culture for use as direct food ingredients. We have seen cultured algae, again those cells grown up in suspension culture and then used as direct food ingredients. And we have also seen fungi. Yeast is the most trivial example, but we have also seen microprotein, which some of you may be familiar with. it is essentially a fungal mass grown in culture and

harvested for use as a protein source.

And then the final example is new plant varieties produced by modern biotechnology. So this is a category of foods that we have been looking at for over 20 years. The specific techniques used to produce the new plant varieties, they all involve some form of genetic manipulation, but the techniques have evolved and new techniques have been introduced over time. The basic framework that we use for looking at these is just to ask ourselves what do we know about the sort of source of any materials that are introduced, what are the properties of the substance that is introduced, what potential effects could be detected by comparing this modified variety or this new variety with comparative varieties. And, then, finally -- and this is an important point -- what is the significance of a material standpoint, whether it is safety or nutrition, in terms of the effect on the food? So many of these modifications to these varieties have no effect on the food at all or have an effect that is not meaningful from either a safety or nutrition perspective.

And so that is sort of something to keep in

mind that was alluded to earlier with this question of, you know, differentiation of cells. Not all of them go to the appropriate differentiation state. After identifying the difference, it is useful to think about what the potential significance of it could be, either from a safety or nutritional standpoint.

So I have covered a lot of ground pretty quickly, but the basic idea here is that we have looked at a number of biological production systems for a wide variety of organisms and materials. And they are complex, and it is reasonable to ask questions about consistency of the process and control of the outcomes. What we have seen to date is generally that it is possible to adequately characterize the outputs of these processes, both with respect to safety and other parameters of interest and to resolve any questions that come up before market entry.

So, with that, I will conclude my talk. Hopefully this has provided a little bit of additional useful context for you to think about in your deliberations this afternoon. Thank you.

DR. McLELLAN: Great. Thank you. That is a

great overview, Jeremiah.

Any particular specific question to his presentation? One. Go ahead, Rebecca.

DR. SHEETS: So when talking about a food ingredient, is quantity a part of that definition? Because you mentioned identification and exposure; in other words, how much you are exposed to. And what I am thinking about is one of the components that is added to large-scale bioreactors is anti-foam. So that is something where you might be able to wash the cells to remove a lot of it, but it is something that might be present. Is it then a food ingredient or does it depend on how much is left over or how much is residual before it is considered a food ingredient or not?

MR. FASANO: That is an excellent question. I think, in addition to revoking the standard answer that it is always case-based when we make these evaluations, I think what I can say is that frequently when we look at food ingredients, there are often constituents that are introduced during the manufacturing process that there may be residual quantities of. Essentially it depends on your level of

analysis. If the thing that you are adding to food is the ingredient, then constituents introduce a new manufacturing process, we would consider it as part of that ingredient assessment process. And, again, frequently the levels of exposure are extraordinarily low. And so we could kind of consider it as part of our overall analysis of the ingredient safety.

DR. McLELLAN: Great overview, Jeremiah.

We are going to hold all further questions until we get into the afternoon session and move on to Emilio. Appreciate you being here. And thanks for giving us this overall from an FSIS perspective.

DR. ESTEBAN: Well, good afternoon. And I understand I am the only thing between you and lunch. So I am going to talk about food safety, not food speed, but I do speak fast. So if you don't understand something, please let me know. All right.

If you walk away today from this talk with anything, it has to be these five bullet points. FSIS has as system whereby we have continuous inspection onsite. Unless the inspector is present, the food is not produced. If it is produced without our

inspection, it is recalled.

Everything we do in the way of standards is led by science. We use science as a basis for anything, any of our programs. And we have three labs right now. That actually test all of the food that is produced, meat, poultry, and eggs, that is produced in this country. We produce data every single day. Everything we do is in real time. So the inspectors have the information, and a product is released after they get the information on the results of that sample.

The program that we have is very flexible. We can add new targets, whether it is biological, chemical, or physical, at any time. And we have full transparency before we use any method. Those methods are publicly available on our website at least 30 days before we start using them so that people know what they are going to be tested for and they know exactly how we are measuring them.

And the other side of the equation also works. All of the data that is generated is posted as soon as possible on the website. So it is both clear on the way in and clear on the way out what we are

getting for that testing.

And, of course, we have ongoing systems that are both for baseline purposes to monitor trends. And we have pretty solid merchant response to our investigation.

As said before, we have about 6,000 establishments that we monitor. We have an inspection force of over 10,000 people. We deal both with domestic and with imported product. And I will maybe explain a little bit more about the imported and domestic is based on an equivalency system. We expect that the competent authority or the company that produces food for import into the United States are equivalent to what we do in the United States. And we go and actually do audits, physical audits, of those places before the food is exported.

We have a significant emphasis on education and outreach about safe food-handling practices. And, of course, we don’t do this alone. We understand that this is a team effort, and we work with CDC, FDA, EPA, and other partners, stakeholders, industry to get for you safe food.

As said before, we have three labs, in Athens, Georgia; St. Louis, Missouri; now one in California, that assist with investigation, national/international outbreaks. We monitor current and emerging foodborne threats. And we provide all of the information that we need to develop our science-based performance and production standards.

On the average, we test about 100,000 samples every year. Those 100,000 samples are tested for multiple things. So we end up generating multiple millions of data points from those samples.

This is just to emphasize that everything is science-driven. And one thing that I would like to highlight with this slide is at the three labs, any sample that generates a foodborne pathogen is tested and being characterized through whole genome sequencing. And everything is done in real time. So for any isolate that we have from someone, E. coli, Listeria, Campylobacter, we go through the whole range of activities, some isolation to serotyping, whole genome sequencing, PFGE. Everything that is possible to be done on the isolates, we do it. And we post that

information online.

These are the six areas that we test for: microbiological contaminants, chemical, physical. We deal with some emerging issues, things that come out of left field. Say, for example, we get information from Europe that there was fipronil in eggs. We promptly develop a sampling program to test for the pesticide fipronil in eggs. We have a pretty solid testing scheme for allergens. And obviously we have a test for identity, which is basically speciation, but it doesn't just stay there.

Okay. For microbiology, in particular, I guess it is about 80,000 samples a year. Those are spread across 60 different sampling programs. So, for example, for something like raw beef, we may have a sampling program for the carcasses, one for the trim, one for the ground, one for the components that go into the ground. The same thing happens, for example, for ready-to-eat products, where we have a system whereby we test the product, the contact surfaces, and the environment where that product is produced.

As I said before, we have daily information.

Not only the lab information is daily, but the inspectors in the end plants need to actually do a lot of documentation regarding the HACCP for the HACCP analysis and create a control point in that plant. Again, their sanitation records go into play. So it is not just a physical product. It is also the physical inspection of the plant at the time of production.

If we do find an isolate from one of those samples, like I said before, we do everything to characterize it. And all of the characterization is done, as I said, in real time, which includes antimicrobial resistance, sequencing, and serotype.

Those 80,000 samples in 2017 generated about 160,000 microbiological tests of both raw and cooked products, including beef; pork; poultry; egg; and Siluriformes fish, which is catfish. And we specifically focused on those 4 pathogens you see up there: E. coli 157 and the other not a157, Campylobacter, salmonella, and Listeria monocytogenes.

This is one slide specific for Listeria. We have a significant effort in that in that we expand not only to test the products, but we include the

environment.

We have done very, very significant work on a harborage on these plants, meaning that in some instances, we are able to trace a current finding to two or three years before, when that pathogen has been residing at that plant for that long. So we have every -- some plants produce three shifts. So we work on all three shifts. And so the sampling is continuous. So for the large plants, for example, on the average, we have a sample every week; for the small plants, about every other week; and for the very small plants, we target once a month or at least when they are in production. What this means is that if there is meat, poultry, and eggs, it has some type of sampling.

That said and given the previous talk that we heard, I would like to emphasize that the sampling programs that are managed by FSIS are verification sampling programs. In other words, the plant, the producer, the establishment needs to have their own sampling process control documentation. Our sample is to verify that their HACCP is under control. So it is verification sampling of the plant's process control.

Just one data chart that I am going to share with you because I don't want to confuse you with data. Overall, if you look up there at the graph on the left for 2014, '15, and '16, for salmonella and Campylobacter, you can see a very minuscule trend. We are making significant efforts in trying to reduce the contamination by salmonella. It seems to be there every time, but we are making some progress. We get a better detection technique, and we find more again. So, you know, the better we are at finding it, the more we find it, the better we do, the more we find. And so it is a cycle.

On the right-hand side, the same thing for ground beef and for beef trimmings and those types of commodities. We do observe a significant progress, downward I hope, on the contamination rates. And these are based on weighted prevalence.

Moving over from what we do in pathogens to what we do in regular chemistry, as you know, we don't set tolerances. FDA or EPA sets the tolerances. We enforce those tolerances. So we have multiple methods, all of which are published on our website. One of our

methods, just one of them, tests for over 90 drugs. And we test those in muscle, kidney, and liver. Violations are reported on the website. And for multiple violations, they, which means two or more, are reported to FDA for potential enforcement, if needed. Those 90 drugs include anything from antibacterials to antifungals to anthelmintics, synthetic hormones, beta-agonists, antiinflammatory drugs. We probably run about 7,000 samples with these methods every year and an additional 7,000 samples that may be tested that are already screened positive in the field that come to one of our labs. In total, 14,000 samples are tested with this type of array of chemicals.

For pesticides, we have a very similar program. About the same number of samples, about 6,000, are randomly selected from healthy-looking animals. And in this case, of course, we enforce the EPA tolerances and limits. The one method that we have for pesticides right now tests over 108. The last version is going to be 135 different pesticides and metabolites, some of which are the traditional POPs, pesticide persistent organic pollutants, to

chlorpyrifos, which seems to be everywhere these days.

The methods are reviewed on an ongoing basis. And we visit with EPA at least once a year to revise the target of the list of compounds. We have an ongoing list that we risk-rank and target the top tier of that list.

We also do physical hazards and pathology. We have a significant effort at every plant. This is the public health veterinarians in those plants make dispositions based on antemortem inspection and if an animal is passed for inspection, then postmortem inspection.

I listed there some food safety conditions and some non-food safety conditions that would cause for us to condemn the carcass or parts of that carcass. Again, we also document and have now probably between 5 and 10 thousand samples depending on the year for samples that we test for pathologies or for foreign materials.

As far as wholesomeness and other testing that we do, we have an ongoing test for speciation. When somebody says that they are exporting or producing

a sausage that is pork, we want to make sure that it is pork and not pork, chicken, beef mixed. So we test both raw and cooked commodities for identity, the same thing with catfish, Siluriformes. We test for Siluriformes to make sure that it is that one family and not other types of fish that are being sold as Siluriformes.

As far as the food, what we call food chemistry, besides water content, we do protein, sodium, fat, soy, a lot of other things. These are just the ones that I put up there for examples.

And, again, these projects are pretty flexible. We can actually add or change things as we need to depending on the commodity that we are looking at.

If we look at the topic that we were trying to discuss a bit before here but cell culture, we would probably look at things like antibiotics, growth modulators, mycoplasma, and maybe on the cell lines or pathology group. So I didn't go much into the way of specifics here because we are early in this game. First, we need to define what we are going to be

looking at. And then we going to have to define how we are going to be looking at it. So this point I just wanted to emphasize the flexibility and depth that we have in our three labs to do this kind of work.

And, finally, I want to emphasize the fact that we are a team. We have a lot of people that we work with and work for; for example, the talk that we had earlier today from Dr. McDermott. The work we do with FDA for antimicrobial residues with CDC with several centers from FDA, several centers, several agencies in the USDA, it is a collaboration. We don't work on our own. This is food everybody eats, and we have to work together.

And I will stop.

DR. McLELLAN: Thank you. Great overview.

We have time for very few questions and then lunch. I have got three starting with Sean.

DR. XIE: It is very interesting to listen to a talk about the whole processing of food safety. Only the last second slide would relate to the cell-cultured food? So it means all of the cell-cultured food will follow the same processing? Then related to this, the

particular example is the allergen. You mentioned it several times. How do you predict any cell-cultured food, meat will have issue with the kids? Because if you take the example of the peanuts allergy, it could be life-threatening for the kids, “You had better take this.” How do you predict certain cell-cultured meat will have cause potentially for allergens for kids or adults?

DR. ESTEBAN: That is a good question. And, actually, it is to the core of the way we run our business. We would work with FDA in this case, consumer groups, industry itself to try to identify what are the hazards likely to occur. If those hazards are likely to occur, they will be part of their HACCP system in the plant that is producing that meet. So we would have to know a priori what those hazards are. We would develop the methods to test for them. And then based on the information that they have generated from that production process, we would verify that they have maintained those hazards away.

DR. XIE: Some of the allergen is a direct cause. Some of the allergen could be the food

metabolism which caused that. Right?

DR. ESTEBAN: Right. And, again, we don't know at this point what the food metabolism might be because we don't have any -- in the literature that I have reviewed so far, we are so far early in the game that at this point, the best thing we can do is prepare the system to be structurally sound to be able to respond when that hazard is identified. At this point, they wouldn't predict them.

DR. McLELLAN: Barbara?

DR. KOWALCYK: Barbara Kowalcyk. Thank you, Emilio, for a good presentation. I have a couple of I think comments, clarifications, and a question.

Since some of the people on the Science Board may not be as familiar with meat and poultry inspection activities, I just wanted to clarify that continuous onsite inspection depending on whether you are doing slaughter or processing will be different. During slaughter, there is an inspector in the facility during the entire slaughter process. The continuous onsite inspection for processing is on a daily basis for a limited amount of time.

DR. ESTEBAN: Correct.

DR. KOWALCYK: And also I wanted to clarify that FSIS does not require producers to have microbiological testing programs, correct?

DR. ESTEBAN: That is correct. They have to have a hazard system. And we can monitor the process and control.

DR. KOWALCYK: Right. So that brings me to the point that you made that your testing programs at FSIS are verification programs, not designed to ensure the safety of the product because that lies with the producer. And it certainly sounds like 80,000 samples a year is a lot, but do you have a sense as to what the power of that testing program is to detect contaminants?

DR. ESTEBAN: Well, good question. And you and I have talked about this before. I think that the key is in your assumption. If the assumption is that we are looking to make sure that every pound of food is safe, then 80,000 is not going to be power enough. If you use as a denominator for your sampling size the HACCP system; in other words, you are verifying that

the HACCP system is working, then the sample size might be appropriate because we have a sample every week for that one HACCP system. I have not done a calculation, but my assumption has always been that we do verification testing. And the verification is that the HACCP system is under control.

DR. KOWALCYK: Right. So I am going to answer. My experience is that the power of most sampling programs in the food safety realm is probably in the 5 to maybe 20 percent probability to be able to detect contamination if it is present. And I just bring this up because the type of -- I mean, in the previous talk, we heard a lot about testing as a way to ensure the safety of these products. And I just wanted to clarify kind of what the role of FSIS' testing program is and also provide context for the other board members as to what the power of these testing programs really is.

It would be also interesting -- we didn't hear yet, and I would be interested maybe later to hear how many microbiological tests FDA does in their food safety programs on an annual basis.

DR. McLELLAN: Dave?

MR. REJESKI: Just a thought experiment I was playing through in my head if we go from a sort of a lab-scale production to an industrial-scale production. So let's assume in whatever, 10-15 years, we have 10,000 bioreactor facilitators in the U.S. that are producing cultured meat. I don't think that is an underestimate. I mean, if you had a bioreactor with a 30-ton output, it can only feed about 7 or 8 hundred people now given our beef consumption. Does that then become a USDA inspection problem? If you are expecting 6,000 now, what happens if we add another few thousand?

DR. ESTEBAN: Well, it is a very good question. I think at this point in the game, we are in listening mode. We don't know how many producers will be commercially available. For example, the most recent change was with catfish inspection. We didn't have catfish inspection before. Right? And suddenly we were assigned to do it by Congress. And somehow we were able to accommodate whatever was in production to be managed with the same staff. So there are ways in which you can actually manage it. I am not saying that

we are going to add 10,000 staff to our staff because that is not going to happen. I can say that we will adapt to whatever the way it comes in. It will never be 10,000 producers right now. If we have 6,000 producers for all of the meat, poultry, and eggs, I don't there would be 10,000 individual producers that will be marketing this product. But if it were to be the case, I guess we would have to go into that environment. At this point, I think it is too early to tell, even if we are going to be part of the regulation or not. That is still up in the air.

DR. McLELLAN: Okay. I have got two follow-on questions. And then we will close it before. So we will start with Lynn and then over to Barbara.

DR. GOLDMAN: Briefly, I think, and as a follow-up to Barbara's point, it does seem to me that one thing both agencies have in common in the law and in regulations is their reliance on HACCP. I think that the questions that are being asked, by the way, are very relevant to that in terms of that HACCP is only as good as the science that we have to understand what are actually the critical points at which things

can kind of go wrong. And what are the technologies that are needed to be in place or the practices that need to be in place to prevent things from going wrong at those points?

So I am kind of excited about our conversation this afternoon, but I think, you know, that the sampling is important as a backstop, but, actually, what is most important is being able to have science to inform kind of, you know, what are the procedures going to need to look like? What are you going to require? And that is going to be I think the rub here because it is very different than using cells to make vaccines or stem cells for medical therapy or any other purposes.

DR. ESTEBAN: Right. I mean, you are correct. Though we have the list of hazards identified, the critical control points identified, it will be difficult to propose a sampling program that covers those because, well, we don’t know why we are targeting it. So it is an evolution. We are learning as we go. I don’t think this will happen tomorrow. Some people would like for it to happen tomorrow, but

it is not going to happen.

So yes, let's work together. I mean, people like you and this board in your jobs, that is where we get the science from that we can do our work. So everybody, like it says up there, needs to be part of this solution.

DR. McLELLAN: Barbara, last comment.

DR. KOWALCYK: So I just wanted to follow up on a couple of things. One, I agree with Lynn that sampling is only one of the aspects. And, of course, one of the questions that I have is, do we really understand the potential hazards associated with this product? And do we have the science to do that?

I also wanted to follow up on the comment about inspection because it is important. Right now, both agencies are very strapped in inspection resources. And I am concerned about the ability for the agencies to meet the potential demand. I mean, FDA currently under FSMA is moving to inspection once every 10 years to once every 5 to 7 years, which pales in comparison to what USDA has. But I also wanted to clarify that USDA regulates 6,000 establishments under

federal regulation. There are quite a few more producers that operate at the state level and are regulated at the state level.

And so one question that I have -- and it just occurred to me -- is, you know, the definition of having a producer being regulated at the state level versus federal level is whether or not their products cross state lines. Are these products going to be potentially regulated at the state level? And do states have the resources to actually implement those regulations?

DR. ESTEBAN: Thank you for that question because it is important. We always focus on the federal establishments and what we do across borders because that is what will go to the news. But we do have, actually, a very large grant mechanism in which we actually have defined some states as equivalent to FSIS. And so we do audits of the labs that serve those establishments. And we do have continuous communication and can schedule samples from those establishments for the states to collect and the states to analyze. So we do have a state component in FSIS

that is not always very, very talked about. It is worth about $50 million. At this point, we have an investment. But it is definitely something that we will have to lean on if we start seeing all of these in-state plants producing food for the state.

So I can go on forever. So I will just stop there.

DR. McLELLAN: Thank you, Dr. Esteban. That was a great overview.

So, ladies and gentlemen, we are going to be breaking for lunch here. I would note we have had a number of slide presentations. Those will all be available to the committee members and to the public tomorrow.

We will come back at 1:05 or so. So mark your calendar. Mark your watch, if you would. Committee members, we will be gathering for lunch behind me in the back corner. And enjoy your break. Thank you.

[A luncheon recess was taken.]

A F T E R N O O N S E S S I O N

CFSAN SESSION

DR. McLELLAN: Welcome back, everyone. I hope you enjoyed your lunch. We are going to continue to be joined by some of our experts from CFSAN as well as our external experts that are joining the board. And we have got a series of six guiding questions. If we can get through those, great. If not, we have got other times we can jump on that.

I think what we will try to do is keep apace, keep things moving. But at the same time, this is the chance to dig in and sort of get both some concerns and hopes and all different aspects of this issue out on the table.

So our first guiding question here is pertaining to the adventitious agents that may be introduced to the culture from seed cells or materials and what sort of risks they may pose to human health; if so, what are these and what tools might we use to effectively manage the risks, reduce the risks, et cetera. So I will open the floor for comment and questions that folks may have. Rod?

DR. BRISTER: So I had a question. When I was reading through the material, it occurred to me that you are monitoring for things that can cause humans harm. And then the thing that I kept coming back to was you are monitoring against what baseline? And that is you are producing a product that presumably replaces meat. Do we have like a human health standard for meat? And that is, do we know, for example -- I assume that in meat, you can find undifferentiated cells. That is how people get primary cell cultures. I assume that there is some load of endogenous viruses in meat. I assume that there is some load of maybe virulent viruses in meat. And so I am completely naïve to this, and I am just wondering if there is some established baseline of what we think is healthy that any sort of new product that is introduced can be compared to in order to assess its own health.

DR. McLELLAN: Go ahead, Lynn.

DR. GOLDMAN: I actually think that there is something useful in that framing, which is that I think that -- well, I think, one, the answer to the question is yes, you know, but, then, it really is, what are

they. So it is hard, right? Because absolutely yes. And I think we have gotten lots of examples from the FDA, you know, that say yes, you know, yes, this is a possibility.

But I think it is very useful to think in terms of the known hazards already with meat that is produced through conventional means -- right? -- and which, if any, of those might also be present in these in vitro systems. I am not even sure if we all agree on what we call this, but, you know, some of them are probably -- there is probably some overlap.

And, by the way, I am not aware. I may be forgetful. I am not aware of any of them being actual, you know, viruses. A lot of them are bacterial and toxins and, you know, various other things. But there might be some. But, then, it is also what might be introduced via the process of producing, you know, in vitro meat that we don’t see, you know, with conventional meat produced in animal production and might not be detected or guarded against using HACCP without having some special consideration for that.

I mean, presumably -- I mean, I will just --

you know, Listeria. Listeria is a very widely difficult pathogen to deal with. And it is something that a lot of -- there are a lot of HACCP guidelines around trying to keep that out of meat, keep it out of the food supply, period. And Listeria also I think could introduce itself, be introduced into in vitro production. I can think of a number of ways that it could be, but, you know, there is a lot of focus on Listeria. But what about things that might be introduced, you know, because they might, you know, get into culture media or substrate, whatever substrate is, you know, other -- somebody mentioned the washing fluids, things that you would not be expecting in conventional production.

DR. McLELLAN: Rebecca?

DR. SHEETS: Thank you.

So the obvious answer is yes. And we know a lot of the kinds of agents that get into cell culture. We also know a lot about primary culture, although not so much from muscle but more so from other organs, kidney, epithelial cells, and so on.

But confining my comments to in vitro-

produced meat; in other words, skeletal muscle being grown in cell or tissue culture, we have to keep in mind that a lot of the risks that we think about are in the context of the clinical use of the product. And that is how FDA thinks about it.

Now, food is not clinically used, but obviously we have to think about it in the context of most people cook their meat. Now, it is true it is not always cooked thoroughly. So we do have to worry a bit about what would be left if it is undercooked or not cooked, but a lot of the adventitious agents would be killed by the cooking process. And then there is the oral ingestion and the fact that when we think about vaccines, we are thinking about parenterals for the most part. And those go directly into the body by passing all of your natural defense systems.

Food, on the other hand, is going to go in through the normal portal, through the normal defense systems. And so most of the adventitious agents unless they are designed to be enteric organisms are going to be digested. There are enteric organisms, and those are the ones I think you would be particularly

concerned about, things like E. coli. Those are things that would grow well in cell culture if they were present. And normally with cell culture, we monitor bioburden, and we handle it aseptically. So you would monitor your source materials, as was described earlier. If you are producing from a cell bank, you will have qualified your cell bank and shown that it was free of bacterial contamination as well as other adventitious agents before you even begin production. And then during production, you would monitor for bioburden.

So I think there are already a number of steps in place for both hazard identification as well as risk management that would be able to be applied in this setting that could mitigate any risks -- I shouldn't say "any" -- mitigate a number of risks that could come from adventitious agents that could come into the process from the source, from the personnel, the environment, and so on. So I hope that is helpful.

DR. McLELLAN: Barb?

DR. KOWALCYK: Barb Kowalcyk. So I wanted to echo some of Lynn's concerns. I think my main concern

here is I don't -- the answer to the first question is obviously yes, but I don't think we actually know enough about what the potential hazards are. And that is what concerns me.

I wanted to add on to your comment because cooking often comes up in the context of food safety. One of my concerns about cell-cultured meats is that people may view them as sterile and they are being labeled as clean. And so, therefore, they may feel that it is safe to consume them without cooking. So I think that that is something that the agency should understand better, is how would consumers handle and consume these products.

But cooking only addresses microbiological contamination of food. It doesn't address toxicological contamination of food. And that is something that I am concerned about based on the readings.

You know, in one of the articles, they talked about adding human growth hormone to the culture medium. And, you know, at what level of residues is going to be in this product afterwards? And cooking,

of course, would not necessarily address that.

So I think that those are some of the things that I have questions about. I think the obvious ones are Listeria monocytogenes and the ones that we already know about in meat and poultry products. But what about these unknowns that are going to be unique to this type of product? I don't feel like I have enough information to assess that. And I would like to know whether or not the agencies do.

And, of course, one way to look at this -- and going back to the NAS report that was provided as background materials for us -- is the use of risk assessment and risk-benefit assessment. And I was wondering if the agencies have undertaken those for this product to date.

I mean, I do know that there are risks. There is a risk-assessment group from both agencies. And I didn't know if they had started looking at this.

DR. McLELLAN: Connie?

DR. WEAVER: Did we get an answer to that?

DR. McLELLAN: Care to comment, Jeremiah?

MR. FASANO: I mean, I think one thing I can

say is that the preceding risk assessment is hazard identification. And that is one of the things that we are engaged in right now with input from you folks.

DR. WEAVER: So we haven't spent any time talking about why and for whom. And I think it matters for some of the details of this discussion.

This summer at the annual IFT meeting in July, we heard speakers from Europe, one of whom showed blueprints of a large-scale commercial plant under construction now. And he said that the first priorities were to develop cost-efficient media preparation. Well, if you are producing the product, the muscle protein product, to feed the world, who is clamoring for more protein in some regions, that is one set of goals. But if you are trying to feed groups that are now not selecting meat because they are concerned of sustainability or cruelty to animals or something, that is a whole different set. You can't be using fetal bovine serum in a media if that is your objective: to bring meat to the ones not choosing animal products. So why and for whom?

DR. McLELLAN: Go ahead.

MR. FASANO: I just want to clarify. I don't think anybody is contemplating that when these products go into commercial production, they are going to be using any animal-derived serum. I think it is all probably going to be produced through recombinant protein production. It is not going to be fetal calf serum or fetal bovine serum. It won't scale for one thing. And then also in terms of marketing, it is unlikely to be appealing to a lot of those folks. So I think it is a reasonable presumption that it is going to be serum-free growth medium.

DR. McLELLAN: Rebecca?

DR. SHEETS: I wanted to focus on -- the first question was about adventitious agents, not about toxins, per se. So I just wanted to focus on that. We actually know quite a lot. I am not going to say there are not any unknowns. We still are discovering viruses. We are still discovering viruses in species we didn't know they were in that were in other species that we knew about. So I am not going to say there are no unknown adventitious agents, but certainly there is quite a lot known in terms of and tests in place for

testing and detecting adventitious agents.

Your sampling question from earlier is very valid. And it is something that I have thought a lot about in terms of vaccine production. And so it would be something that would have to be considered in terms of in vitro meat production or cell culture-derived skeletal meat production, whatever you want to call this, but, you know, you could develop a sampling procedure or a sampling plan that would allow you to have some level of confidence about adventitious agents.

There are some assumptions that are made about, for example, homogeneous contamination. A lot of times when viruses get into a culture, they are not apparent at first, but then they take over the whole culture. And so any sample is going to be positive; likewise, with a lot of bacterial contaminations or even mycoplasma. But there could be a stage at which you would monitor where you would have, you know, beginning of an infection and every sample wouldn't necessarily get positive. So you would have to develop a sampling plan that would be appropriate for this type

of product. But I think there are a lot of tools in terms of -- and I wasn't sure if you were talking about risk-management tools or you are talking about testing tools, but there are a lot of testing tools that exist already for therapeutics and for vaccines for cell culture that could be used.

As far as what kind of tools, risk-management tools, I know in my industry, we tend to use more of the FMEA approach, rather than HACCP, but I think that probably HACCP could be applied, you know, as far as risk-assessment tools. So I wasn't sure of that question, whether it was asking about tests for adventitious agents or risk-assessment tools.

DR. McLELLAN: Annalisa?

MS. JENKINS: So just from the perspective of an industry working in therapeutics for a number of years, clearly the answer to the question is yes. But, again, just reinforcing the previous comment, I am mindful of the fact that there exists within our industry a broad and deep knowledge on this topic. And as I listen to my friends from the agency, previously from the agency, I am reminded of the fact that there

is a large amount of science that has gone into the production of cellular-based therapeutics or the use of cells in the context of therapeutics. And I am just hoping that the industry that is emerging is prepared to talk to and learn from that experience so as not to reinvent the wheel because the standards that are set for the administration of the cellular-based therapeutics, often into patients that are largely immunocompromised, are extremely high. So when considering this topic, if you start with the highest standard, work through how you can sustain and ensure that, you can then based on your risk-assessment tools and the standards that you wish to set in this particular context, I think probably come to the right solution.

DR. McLELLAN: So that is actually a good segue to our second question because it really points to the issue of experience. What have we seen? And, Rebecca, maybe I can put you a bit on the spot to reflect on, quite frankly, where has it gone wrong? And what did we learn from the going wrong? That would be a very helpful I think perspective.

DR. SHEETS: So thanks for putting me on the spot. So quite a lot is known. I mean, obviously cell culture has been around since the 1950s. It really was a tool developed by virologists so that we can make viral vaccines. Obviously it has been expanded to therapeutics in the ’80s with biotechnology. And so there is a ton of experience. There are bioreactors that are on the 20,000-liter scale that are run right next to another one next to another one next to another one, you know, just fantastically amazing. Plants that have these, you know, spic-and-span, sterling-clean environments and lots of bioreactors, and they are making important medicines.

So it is something that is done every day, and it is done successfully every day. And there have been contamination events. They are rare. There are probably some that have happened that haven’t been reported, but there has been an effort to get the therapeutics industry at least together, too, because they tend to use a more standard cell platform. Vaccines are made on various different cells; whereas, therapeutics, a lot of them are made on cho cells, for

example. And so they have tried to come together, privately as well as publicly, to expose the cell culture experience and the contamination events.

They are rare. They do happen. There are viral contamination events as well as other organisms. So they do occur. It is much worse with primary culture. So, for example, flu vaccine is made in eggs. And batch after batch gets thrown out every year because of bacterial contamination in the eggs, you know. So that is much worse than starting from a master cell bank or working cell bank, where you have qualified it and shown it to be to the extent of the testing free from adventitious agents.

So as far as scaling events, scale-up is not easy. Like I said, you have to start adding things that you wouldn't have added at small scale, like anti-foam, you know, because now you are agitating large volumes and you are generating foam. And so, you know, scale-up is an art, and it takes a really good cell culture team to be able to, you know, optimize the media.

I agree that it is very unlikely given the

needs of fetal bovine serum for the medical industry already. I think if the food industry starts tapping into that as well, you know, there will be a black market in fetal bovine serum, and it won't be fetal bovine serum, you know.

So I just don't think that that is going to be feasible for the food people, in addition to the fact that, you know, if you want to avoid being a GMO, if you want to avoid -- if there are certain things you are trying to do and you are marketing to avoid being an animal -- it is an animal product, but it is not, you know, injuring animals or it doesn't have animal protein in it except for the meat. You know, if it is not having extraneous materials, then you are not going to use fetal bovine serum if that is what your marketing ploy is, if that is who you are -- you are trying to attract vegetarians who want to eat turkey for Thanksgiving or whatever.

So I think that as far as scaling effects, I think fetal bovine serum, it is only going to be able to be used on small-scale and probably not for commercialization unless you have a very tiny market.

So I think that removing those elements that are animal-derived and removing things from primary sources will reduce your risk of adventitious agents particularly and then as part of that question, the likelihood of risks. So there are going to be new risks.

I don't want to stray from adventitious agents. We are going to get in the next few questions to the other kinds of risks. I don't think that you are going to have a greater risk than you have, for example, with risk of E. coli in hamburger meat or, you know, current risk of salmonella in chicken or whatever. I think you are going to have better control, more consistency of manufacture with a cell culture produced.

So I think you can control risks better with a cell culture-produced product. You are going to be using more defined media. Then you have to look at, well, if we are using defined media, are there any recombinant products in it? And then you have to start worrying about, well, now is it a GMO or not a GMO or it is not an organism because it is meat? You know,

those are going to be labeling issues for FDA to sort out.

So I will finish with that.

DR. McLELLAN: Okay. We have a couple of questions, but I will take a chair's prerogative and inject one for Jeremiah. It really comes to your question of what is this. If we choose to regulate this as meat, does this have its own identity or do you somehow go back to the originating source cell? Care to explore?

MR. FASANO: I think those are excellent questions that we are probably not going to address here, but what I will -- two brief comments about that. I think the first one is just all comparative analysis is useful, but all comparative analysis is partial. So it is useful to think of things that are referenced for comparison when you are doing safety assessment, but rarely does anyone reference a complete parallel to the thing you are comparing. So it is useful when you are thinking about what you are comparing to be clear about what the risk is you are trying to compare so you can understand it more clearly. That is something we have

seen in other areas.

The other thing I will just mention in terms of your recombinant proteins in food, there are lots of them already. We generally don't label them. You know, they are labeled as ingredients. But that is already widespread practice.

DR. McLELLAN: Okay. Let's come back to Rodney.

DR. BRISTER: Rodney Brister. So what I was getting at earlier was right now we have a testing regime based on mostly enteric organisms. And as I understand that, it is because the cow carries the organism or the chicken carries the organism into the slaughter and the organism is then spread from the gastrointestinal tract to the meat. What I was trying to get at is that when we were discussing cultured cells or cultured meat, that there is a chance for new sorts of organism to now be imported in the regulatory environment. And so I am drawing on my experience when working with CBER on sequencing-based technologies to detect agents within vaccines and other biological products.

So there clearly are cases in history where viruses were missed and where products went out to the public that included those viruses. So that is clear.

And I will say we are discovering viruses every day. There are 20,000 species of viruses in the public databases today, and there are people who make a living going around and saying, “That is 1 percent,” “.1 percent,” “.01 percent of the number of viruses we expect to find.” Now, there certainly are some caveats to those statements. And I am not sure I accept those sorts of statements, but it is important to recognize that there are many things we don’t know. And, for example, two years ago, if I told you our brains were filled with herpes virus, you would say I was an idiot, but today there are now people claiming that 50 percent of Alzheimer’s is connected to herpes virus.

If I told you that all of us carried these little things called circoviruses 10 years ago and these would be one of the most abundant viruses, in the millions that we know of in vertebrates, for that matter, that we know of, you would say, “Well, that is kind of interesting. What does that mean?” We don’t

know. We still don't know what the role of these things is. And we are talking about putting cells under stress. That is part of the regime of transferring a primary culture into something that is -- someone else can speak to this who has more knowledge than I do, but as part of the process, the cells go through a transformation. And those transformations are sometimes associated with, you know, endogenous viruses being activated and other things like that.

So I absolutely agree with the previous statement that Becca made that a cultured environment gives you the chance to monitor things in real time. I absolutely agree that if I were building, you know, the scale-of-this-room environments to have cell culture or to have complex cell-cultured meat products, it would be advantageous to me to be monitoring constantly because a lot of money goes down the tube if something gets infected. I am concerned that we just don't understand the baseline yet. So do we have the technology to do it? Yes. Do we have the knowledge base to know what is important when we do it? I am not

sure yet.

DR. McLELLAN: Bruce? I will just remind everybody to introduce themselves when they first speak.

DR. BRISTER: Thanks.

DR. PSATY: Bruce Psaty, Seattle. My ignorance of this area is both broad and deep. I come at this from the point of view of drug safety. And we have had some humbling experiences over the years. You would take a drug like fenfluramine and phentermine, and they wind up showing valvular heart disease and pulmonary hypertension. We did not anticipate this, and there was no way of anticipating it.

So I think the experience in drug safety is that there will be basically unanticipated risks, and that might argue for some sort of post-marketing surveillance, which has been quite effective in the drug area. I don't know if it is possible here in any way, but our ability to predict risk is sometimes limited.

DR. McLELLAN: Sean?

DR. XIE: I have to come back, when the

commissioner talked about regulatory policy. So it doesn't matter what kind we do. I want to ask, number one, in upstream, we do. So what kind of source to express cell culture? Is this would be laboratory-regulated like BSL-2- or BSL-1- or BSL-3-regulated?

For example, at my lab, we do a lot of regular virus experience for proteins, G protein couple receptors expressed purification. A lot of times, we get a contaminant. Sometimes we even grow very well, at the end, we have got a protein. We are excited about it. We find out that one of the base pairs was missing during the cell growth. So a lot of variables will be later on will cause it hard for industry to reproduce.

So I was wondering, number one, what would be the biological level to regulate? Would it be 1 or 2 or 3? Then number two is the final production will be GLP-regulated? Because if those trip in, that will cost industry very high for production, the cell-cultured meat.

MR. FASANO: Maybe start with the second one and then work backwards. I mean, in general, we have

an expectation of good manufacturing process, which we have a lot of material on that is available. And so I think that if you are making food, a good manufacturing process would be I believe the expectation. That is often specific to the materials and the process involved.

In terms of biosafety level, I mean, I think you would have to look at what are the, you know, plausible risks in terms of a manufacturing facility. I mean, these -- I think that I can't answer that question, but I think I would say that, as with all of these things, you would have to ask yourself, what are the plausible risks from the production process, either, you know, work a level or

DR. XIE: What that means is FDA would come with the regulations. If you grow those cell-cultured meat, we will have meat a certain level of biological safety lab requirement.

MR. FASANO: I mean, I think it would have to be safe as food. Right? If it was something that FDA was involved in regulating, it would have to meet the criteria for food safety. I mean, if you are going

back to the definition of food that we talked about early on, if you are eating or drinking it as food, then it is food. It has to meet the standards set forth in the act.

DR. McLELLAN: Rebecca?

DR. SHEETS: Yes. Rebecca Sheets. I just wanted to comment on something Rodney had said earlier. It is true that there have been contaminations that have occurred and that were present in products even that got on the market. Most of the therapeutic contaminations that have occurred were before the product went to the market, but there have been some vaccines. And we have actually published a series of four case studies of that happening. Again, very rare in terms of our case studies, 4 case studies since the 1960s. So it is not a common event.

That is what I want to assure people, is that yes, it can occur. It does occur. You have to watch for it. You have to be vigilant. You are absolutely right. New viruses are being discovered all of the time. And we are discovering that viruses that we didn't know were in certain species are present. And,

you know, like you said about the circovirus, even tissues that we didn't know that, you know, were susceptible to viral infection. So we are constantly learning, but we have to make decisions based on our knowledge today as well as, you know -- so one of the words that you used earlier was reasonably foreseeable. And so I think we have to reasonably foresee that there are unknown viruses but also acknowledge that we have to make decisions in terms of what we do know at this time.

DR. McLELLAN: Tony?

DR. BAHINSKI: So we had talked about the number of samples and the sampling size but, you know, even going beyond that to the specific test that you might utilize. And, again, it is my ignorance. You know, what is the sensitivity and the rapid turnaround? So you talk about real-time testing. How long does it take, you know, say, for a bacterial culture or with, you know, the genetic sequencing? Can you get, you know, a rapid turnaround time for that test? Something you mentioned just now is like catching -- you know, before the product actually leaves the loading dock,

rather than, you know, while it is still there and you can actually make a call whether to ship or to not ship and, again, just the timing of that.

DR. McLELLAN: Go ahead and answer.

DR. BRISTER: So with sequencing technologies, we are talking hours. And so what I mean by hours, sample prep sequencing and analysis. And depending on how fine-tuned your analysis is, you could imagine a couple of hours for just a sample analysis. Does it contain this marker gene that I think is pathogenic, which is similar to what is being done with the bacterial pathogen pipeline now that we heard about earlier? And then if you found something that was potentially problematic, to go and do a full-scale analysis, go back 24 hours, you should have based on, again, the experience in the pathogen pipeline, a fairly rigorous answer.

DR. GOLDMAN: If I could add?

DR. McLELLAN: Okay, Lynn.

DR. GOLDMAN: An issue always, you know, when it is an agency doing it, there is somebody out in the field getting the sample. Before you have the

possibility of doing an analysis, the sample has to be collected, has to make its way to a lab, has to be processed and all of that. So we don't really even have field equipment for DNA extraction and stuff like that. So I think that there is just a lag. And when you have stuff that is ready to be shipped, that creates an issue. And this is just a challenge, period, you know, with the whole food safety system.

DR. McLELLAN: Okay. Let me go to the back table, Carolyn, and then over to Annalisa and then we will come over in this --

DR. WILSON: I was just going to say one quick thing, just that in the cell therapy world, you may or may not be able to freeze the cellular product, which is a big difference. And so there is a variety of contingencies that we develop in those types of products. But presumably in the meat world, if you needed to do more extensive testing, you could presumably freeze that product while you got the adventitious testing done. There is a variety of assays, in addition to nextgen sequencing, some of which can take weeks to get results.

DR. McLELLAN: Okay. Annalisa?

MS. JENKINS: Annalisa Jenkins. I would just like to take us back to the comment that was made regarding the early phase, relatively young phase of development of the process and the anticipation that further innovation will take this into a serum-free environment. So I had a question, actually, about how in the food context you are thinking about progressive regulation because, of course, in the therapeutic space, we have increasingly a pragmatic progressive review process. There was risk so largely understood and evolved. We have a selective approval process, but it is on the basis of I think a robust understanding of a monitoring program once the product is commercially available.

So how are you thinking about this in the context of food? So if a manufacturer felt that at small scale, using, say, the bovine serum, just using it as one example, felt that they could go commercial, would that be acceptable knowing that, you know, the industry would be constantly innovating to larger scale and potentially understanding, you know, more about the

benefit-risk of an evolved process? I just wondered how you are thinking about that.

MR. FASANO: I mean, one thing I just want to clarify before I forget, I mean, when we are thinking about all of this -- and this is definitely different from the therapeutic space -- we are not really doing risk-benefit tradeoffs, right? Everything has to meet a reasonable certainly no-harm standard. And so that is kind of the standard we are testing against except for substances that are naturally present.

I think for any manufacturing process, we actually have a guidance we put out a couple of years ago where you are making a change in the manufacturing process and, you know, does the usual FDA thing of recommending consultation to talk about potential impacts, but, really, ultimately what we would focus on in any case is the properties of the food that would come out of that.

And so I think when people make changes in manufacturing processes, like, for example, for an ingredient or where the properties of the ingredient change because of some aspect in the manufacturing

process, we sort of would apply our regular standards for food ingredient safety.

In many cases, particularly if it is a GRAS conclusion -- right? -- I didn't talk about this earlier, but if you are concluding that the intended use of something is GRAS, it means there is evidence that is publicly available that shows that the intended use is safe and there is evidence that there is a consensus among the food safety community that the evidence shows the safety of the use. And so that test doesn't rely on any particular piece of data, but it relies on data that is both publicly available and that the qualified experts would agree shows safety. And so that is I think the context in which we would tend to think about safety of a new ingredient or a new manufacturing process.

DR. McLELLAN: Go ahead and follow.

MS. JENKINS: Yes, just as a follow-up. Thank you for that. Because this is so new and, of course, we are having this debate because the science is evolving, are you, therefore -- and I understand this is all about risk. It is really about risk and

the standard one sets and how one thinks about setting those standards and then the tools available to measure and monitor. So are you thinking that this industry is going to evolve with oversight that evolves from more intensive monitoring in the initial couple of years, then fading away as the science evolves and the data around safety and risk becomes available or are you intending to apply today's framework for monitoring of safety and risk based on, you know, what we have at hand today? I just wonder what the philosophy -- and it may be that this is, again, part of what we are talking about today. I just wondered your current working hypothesis around that question.

DR. MAYNE: Maybe I will jump in. I would say why we are here today is to understand the risks. And that is the first piece of it. And then whatever regulatory framework that would be contemplated by FDA, USDA is going to be informed by the science and the risks. So we keep jumping ahead of the risks and going to the regulatory framework when what we really need to understands is what are the risks. And that is why we are convening you guys as the Science Board to help us

on that. So if we can really drill down that, that is what is most helpful to us in terms of how we would then respond as regulators to those risks. I know it is hard to start with the science, but that is where we really need to be.

DR. McLELLAN: Barb? I think you were next, and then we will come back.

DR. KOWALCYK: So I wanted to just address a couple of comments that had gone around, but first I would like to respond to yours. I think from my perspective, my concern is we don't fully understand the risks and that we need a lot of science and research to be done to fully understand those.

I agree with Annalisa. I mean, she is coming from the perspective on the drug side of things. You know, there are lots of animal models that are used initially when testing a product. Then you move to phase 1. And then you move to phase 2. And those are very heavily focused on safety. It is not until you get to phase 3 of a product development do you really look at efficacy.

And so my concern here -- and this is why I

have brought up the different paradigms between food and drug. In drug, you have to go through that process because the hypothesis is that the drug is not safe until you prove it is safe. On food, we tend to put it out there and say, you know, “It is safe” until we find some people that got sick.

I am saying I don’t know. I don’t know the answer. What are all of the risks? I think that there are some very obvious ones. Listeria monocytogenes is one. It is an environmental pathogen. I would fully expect it to be present in whatever establishment is producing these products. But I think that there are other risks that we don’t know about, and I don’t -- I am very concerned that we haven’t done the science yet to fully understand those. Okay? And that is the one comment that I had.

The second comment that I had, I wanted to go back to the testing. This is a question. I know we are getting ahead of ourselves, but the testing is a really important part to understand what the risks are. And we are going to have emerging risks that we -- even if we do all of the science in the world right now, you

know, 10 years from now, there are going to be new emerging risks that are going to happen and sampling strategies and microbiological testing helps us identify those.

One thing that I have been taught -- and I am not a microbiologist -- is testing in food is very different than testing in other products of other -- you know, different than testing in blood or human serum, whatever. It is a very complex matrix. And one of the questions that occurred to me as we were talking about how to test for these, is this going to be end product testing or is it going to be cell bank testing because those scenarios are going to be very, very different? And that is something that we will have to consider.

And then the final thing is, is while I understand your point, I think, Rebecca, about these being very rare events, most failures in the food safety system are very rare events. But given the magnitude of the amount of product produced and the number of times we eat a day, those small failures or 1 percent failures can have a huge public health impact.

And I think that that is something that is really important to keep in mind.

Finally, I am going to come back to this risk assessment or risk-benefit comparison. One of the things that -- and it is not really I don't think addressed in any of the questions that we have -- is the whole premise of going down this path is that we are going to produce food in a more sustainable way than what we are currently on, more sustainable for the environment.

But I heard some things today that made me a little concerned, like single-use plastic. If we go down that road, are we really going down a road that is more environmentally sustainable or is it just creating different environmental risks? So we are moving away from the problems of manure and all of the water contamination, and we are moving to a different type of risk.

And my concern, I don't know the answer that. I think those are very good questions that we have to ask. But I get very worried about unintended consequences. And I don't want to come back 20 years

from now and have the younger scientists saying to us, "But you never thought about that."

DR. McLELLAN: Rodney?

DR. BRISTER: So I just wanted to follow up on a couple of comments earlier. One thing to think about is the technology is rapidly advancing. And this is seen in, for example, the Ebola outbreak and the Zika outbreak, where there were people with handheld sequencers in the field generating data immediately.

Now, there are costs and benefits to doing that sort of analysis. The sequencing they got is somewhat dirty. It is based on a technology that is somewhat error-prone. But if you are asking well-defined questions, that may be enough to get an initial answer.

And I think the comment I guess in my mind -- I am going to end this with a question back to FDA. You know, in terms of production, you can imagine many points where you can test. But I would argue right now that maybe we should be talking about many points where we can sort of figure out what the baseline is, what the basic stuff going on is, what we expect to see in a

sort of open-ended way before we start refining the questions into bite sizes that can be addressed by inexpensive and very fast technology.

And so when I was reading the materials, one thing that struck me was that with sequencing technologies, they work best when you know what you are after, what you are trying to measure. But cell-based technologies, like CPE or something like that, you don't really have to know what caused that. You just have to know that, you know, you have an assay that reveals when a virus or a bacterium is in the culture and it has a deleterious effect on that culture. I think that is a really good thing to know.

So there is some rationale behind having multilayered tests. There is some rationale behind sort of doing testing in a way where some of it is real-time and some of it is after the fact.

And so I guess my question to FDA is that I have been involved with other FDA matters before. We were discussing using next-generation sequencing in the context of making biological, but I don't really know where the FDA is in that because all of the materials I

read about FDA requirements were still very much focused on either cell-based methods or in some cases PCR-based methods. That is in the materials we were given to read.

So I am sort of curious where that is. And is that something FDA sees going forward as something useful and something where they are making progress and beginning to understand the technology and apply it?

DR. McLELLAN: Carolyn?

DR. MARKS: So thanks. This is Peter Marks. Thanks.

So although not many people use next-generation sequencing and submit it to us, submitting those data are completely acceptable. And just in listening to this discussion, one thing I think we probably would want to take as a supposition if we are thinking about this is that whoever starts making cell cultured meat in culture is going to use the latest technology in cell culture, which means they are going to use sterile process with in-process controls, where they are actually generally able very early on, before even a culture reaches full density, to understand if

they have got a contamination. That is why any good cell culture, even the best facilities have a certain failure rate, which is expected because you are dealing with culture media that grows bacteria, just like it grows mammalian cells.

So there will be a failure rate. But there are process controls. And next-generation sequencing might be one of those in-process controls. Given the rate that data can be generated, one can imagine that one would be sampling as you had in-process before you got to essentially confluence or harvest of your cell culture. And that is what we would expect, I think.

DR. MAYNE: Maybe I can a little on the food side. We are, as you know, using a lot of whole genome sequencing right now for the outbreak investigations as well as environmental monitoring in plant. When we go in and do inspections, we often do significant numbers of swabs to look at the environment that the food is being produced in. If we get cannot rule outs from early on, we move straight on in to try to identify what pathogens they are. And if we find a pathogen, we sequence. As you know, we load it up into the NCBI

database. So we are continuing to build up that database. Currently we have over 200,000 sequences that have been loaded up into the genome tracker database. That is wonderful information that we use on the food side to help assure the safety of the food supply.

How it would apply to these products, you know, again, we are trying to figure out what that would look like going forward, but we do, in fact -- you asked about PCR-based tests. I mean, we use whole genome sequencing when we have pathogens. And that has really been a game changer in food safety, as Mark and others will know for sure, Barbara.

DR. McLELLAN: Dave?

MR. REJESKI: I was trying to sort of put myself into the shoes of a consumer going in and getting ready to buy this product and sort of listening to this conversation, where what you hear is “We don’t understand the risks,” right? And I think the important thing to remember is this discourse is in the public sphere already. It is not coming down the pike and years from now, people are sort of -- they are

hearing about this constantly. It is in the media. We just did a big media analysis. Virtually every major country is talking about this. So it is not just a question I think for the FDA or the USDA or even industry to figure out what the risks are but how to communicate them. The consumers don't expect a zero-risk world. Right? So the important thing is that you have to be very clear about what you don't know and what you are going to do about it. Right?

And this point that you brought up about, you know, what happens 10 or 20 years from now, there is this kind of Trojan horse phenomenon called "We are going to let this stuff into the market, and then it is going to do something bad." That is a very powerful cultural narrative.

So people are going to want to know, you know, what happens if something bad happens? Post-market surveillance is really important to deal with that. And I know from sort of focus groups we have done, there is this sort of "Who do we trust to take care of this?" The FDA comes up very high. So they are going to come to the FDA, right?

So I think I am just saying that this is really important, not just to understand the risks but to figure out, you know, how do we talk about them because this is going to have a huge impact on market development and the speed of market development and consumer acceptance? Be honest about what you don't know about the uncertainties and kind of how do you deal with it? What kind of things are we putting in place? What is the surveillance, the testing, whatever it is because there will be risks associated with scaling, the distribution of production, a lot of things that we can't predict? All right?

So I think that is -- I am just kind of making a plug for sort of getting ahead of it, both in terms of what you are doing now in terms of risk identification but just communicating to people because I think people will come to the FDA, which is good news because the trust is still I think very high. But they are going to need some sort of --

DR. MAYNE: Maybe I can react a little bit. I mean, I spoke earlier in my remarks about the notion of consumer confidence. And I do think it is really

important. We can go down pathways and say there may be viruses we are not even aware of out there. Well, that is true for conventional foods today. That is not unique to these products. That is true in the conventional food setting. And we have been regulating in partnership with USDA the food supply, you know, for a very long time. And we, as we have all indicated, have a very safe food supply.

So I think one of the things that would be especially helpful to us is, what are some of the unique risks in this particular setting that we have not encountered in the traditional food setting or that we have learned from the biologic setting that would really help the food side of FDA working in partnership with USDA to really understand what would be the best regulatory framework to address that.

I would agree it is not zero risk. It is a reasonable certainty of no harm is the standards that we use, you know, in the food ingredients, in our determinants of food. So some dialogue around that would be helpful because we all know zero risk is not something that is achievable.

DR. McLELLAN: Lynn?

DR. GOLDMAN: Thanks for that. That is somewhat what I was going to say, but I just wanted to go back to a couple of earlier points, one being, you know, for the cell culture experts to remember that, even though meat is eaten cooked generally, but sometimes it is not. There are dishes where it is raw. But also a problem in food safety is that raw meat touches other things that then end up having -- you know, there can be actual pickup of microorganisms and other things, that they are then transferred to other foods that are not cooked. And nobody does that stuff perfectly in their own kitchen -- that is just, you know, the way it is -- or in restaurants. So you don't want to have -- but this is true with conventional food as well that that is why. That is why we regulate, you know, for pathogens that are killed when you cook them. It sounds stupid, but it is not because there are a lot of people who have been killed by that.

So I think that one of the points that keeps coming up and why it is so hard for us to answer the question that is being brought to us is that I am not

sure that we have enough experience with this kind of very large-scale application of these technologies to understand even what you have to do to make cells grow and thrive when you are trying to do this at a very, very large level. And so to some extent, I hate to say this, but there is going to be some learning through doing because I think as the industry moves forward to try to scale these things up, they will find that there are things, I would guess, that they have to do to be successful to do these at larger-scale that will bring in elements that we don't even have, you know, in the things that we read because nobody is doing it.

DR. McLELLAN: Okay. I have got Leah, then Rebecca, Bruce, and Barb. Leah?

MS. STITZ: My question was actually for Rebecca. On those four case studies that you mentioned, were those cell cultures already including antimicrobials and other items in them to prevent contamination and these failures happened in spite of them?

DR. SHEETS: If I may answer that first? And then I will go back to my comment. So the four case

studies included the SV40 contamination of primary monkey kidney cells for the production of polio vaccine. So the SV40 came from the infected monkeys. Okay? So while there may have been antibiotics present, there were no antivirals.

The second case was finding bacteriophage that was residual from the introduction of fetal bovine serum into the cell culture and prior contamination of the events sterilized fetal bovine serum with bacteria. So yes, the fetal bovine serum was sterilized, but that didn't get rid of the bacteriophage. It got rid of the bacteria.

The third case study was finding the enzymatic signature of endogenous retroviruses that are present in all organisms in some form or another in avian culture-derived vaccines. And so because these are endogenous, there is no way to prevent them. It is just it wasn't expected to find this enzymatic signature because a less sensitive but widely, you know, conventional test had not detected it and it was only when a PCR-based test was available was it detected.

And in each of these cases, I will just say there were not human pathogens. Okay? And then the fourth case, also not a human pathogen, was the finding of circovirus, which was a known agent but was not tested for in a rotavirus vaccine. And it was present from contaminated trypsin, which was animal-derived. So each of these were viral examples. So there were no antivirals used. And each of them came from some kind of primary source or from an endogenous source. So my comment was there was a statement made, you know, “We don’t know the risks.”

I just want to go back to the fact we are talking about adventitious agents. So there are other risks we haven’t talked about yet that we are going to get to those questions. But we actually do know a lot about adventitious agents. We don’t know every virus that exists, but we do know adventitious agents fall into categories: bacteria, fungi, mycoplasma, mycobacteria, viruses, TSE organisms. You know, so we know about adventitious agents. We know a lot about them. We have been worrying about them since the 1960s, when SV40 was found in polio vaccine. So I

don’t think it is fair to say we don’t know much or we don’t know anything or “I don’t know what is going on.” I think we do know a lot.

And we can identify risks. And we have reasonably foreseeable risks knowing we don’t know every virus that is out there. You know, they are still reasonably able to identify what the risks might be. So that is the message, the consumer message, I want people to realize, that we aren’t completely ignorant about adventitious agents. We do know a lot about them. Nobody can say they know everything. I wouldn’t be a scientist if I said I knew everything, but, you know, we do know quite a lot. So I think we can identify risks based on what we do know.

DR. McLELLAN: What we will do here, Bruce, I am going to ask you to close out this portion here. We will roll to the next set of questions, and we will take a five-minute stretch. So if you would?

DR. PSATY: Okay. This is Bruce Psaty. I agree with you. In a sense -- and this goes back to Barbara’s point -- the question is, how are these risks going to be managed over time? The biologics area

knows how to do this. And are you going to start with biologics and step back? What are the complications as you move up to massive production? So I think this is known. You know how to manage the risks in the setting of biologics. But this isn't going to be coming out of Biologics, right, that division? How much are you going to adapt of those processes? And how much can you sacrifice and maintain safety?

And that is maybe Lynn's point about kind of learning as you go along because there may be some steps that you can step back from safely. There may be others that are not safe to step back from. And we don't know that at this point.

Thank you.

DR. McLELLAN: Thanks, Bruce.

We are going to take a five-minute stretch right here. We will roll to the next set of questions. And we will be back at it in just a few.

[Break.]

DR. McLELLAN: I think it would be good if we got started here. So I would ask you to join us at your chairs, and we are on to our second block of

questions concerning substances used in the cell culture media as well as the structural material. And these really circle around the idea of, one, informing ourselves as to what these might be; and then asking the question as to safety issues.

So let's go ahead and start. And, again, I guess I would reach out to one of our experts here. If you could maybe help us with identifying the kinds of substances used in cell culture? Rebecca, I hate to keep coming back to you, but I will come back to you just to start. And you can punt if you want or get us started, if you would. Thank you.

DR. SHEETS: Okay. I will try to get you started here. Well, I think that Leah gave an excellent presentation this morning that gave us a sense of growth factors. And hormones and things like ferritin are added. S vitamins and nutrients, all the amino acids are added.

In terms of meaningful amounts in the finished product, that depends on the processing after harvest. So I don't know that any of these substances would necessarily be there. It is possible that one

might add antibiotics to the culture, particularly if we go back to what Leah presented about starting with a biopsy and then you are taking that into a culture and then you are making a cell bank. Those early passages would probably be in the presence of antibiotics because that primary source could be contaminated. And then the cells that grow out and your establishment of a cell bank, you would presumably then wean it off the antibiotics and not have antibiotics in production. At least that is the way we would do vaccines or therapeutics, although I shouldn't leave anybody with the impression that there aren't vaccines that are made that have antibiotics in the culture media. There are some. But a lot of products are made so that there are no antibiotics left.

So would that be, those trace amounts be, meaningful? Probably not, but I don't know. I think a lot of this hinges on what you mean by meaningful amounts. But there are a number of substances.

I think the other thing we have to think about, though, is that a lot of the substances are things that are already present in food because we are

talking about cells that -- you know, they are going to make proteins. They are going to make lipids. They are going to make carbohydrates. And we digest all of those things. So I think that that is not from the culture media, per se, but from the culture itself. There are going to be nucleic acids. We will digest them.

So I am not sure that there are substances that are of particular special concern that would be from the culture media unless it is something that came from the recombinant process or from the extraction process from where you got the well-defined media. So it would be things that came from the process to make the separate ingredients that would then go into the media, rather than the ingredients themselves.

Does that make sense? Okay.

DR. McLELLAN: Bruce? We will move right on to Annalisa, then.

MS. JENKINS: Addressing the first question, I would like to just reinforce again from -- we have a lot of experience in the manufacture and expansion of cells for use as therapeutics, moving a little bit

beyond vaccines into cells that are used in degenerative processes for regeneration.

And I guess my answer to this question would be in the reading that was provided, there was nothing in there that I could see that was unusual or something that I hadn't become familiar with in the context of manufacturing cells for therapeutic uses, first thing; and, secondly, in this case, nothing there that I feel that we haven't already addressed in terms of robust assays and ability to quantify and, therefore, by definition ability to understand a) elimination or absence of and b) levels that we would be comfortable with for use in human therapeutics. So that is how I address that question.

DR. McLELLAN: Cynthia?

DR. AFSHARI: Yes. Cindy Afshari. I would just agree with Rebecca and Annalisa that I think, you know, in terms of a lot of the substances, we will have had experiences in ways to look at those. I guess some of the ways that may be different in thinking about it is I don't know in the end, you know, the purification process -- and I know you brought that up, Rebecca --

may introduce some things. I am also thinking about whether we would ultimately concentrate certain materials and would certain materials change kind of the cellular content. So if you think about sugars, for example, I don't know what is going to happen, if you have, you know, glucose in your media, how that is going to impact the cells and what point would that final product maybe look different than meat, so to speak, in terms of sugar content.

You know, one of the points that Barbara has made a couple of times has been how are we going to regulate these products. And what is interesting with the cellular therapeutics is we have our certain specs, our release criteria, and we know what we are dosing with. Here I think in the end, we may have a release criterion. We may have characterized it, but in the end, we are not necessarily dosing a prescribed amount. There is not a label necessarily. And so when you think about, you know, this is more on that side of tobacco or alcohol, where you can consume as much as you want to consume, it is an individual choice. So maybe how we look at some of those impurities, so to

speak, or the contaminants or the byproducts that carry along, we can learn a lot in terms of the science from the cellular therapeutics, but in terms of the back end, the delivery, and ultimately regulation will be a little bit different.

DR. McLELLAN: Tony?

DR. BAHINSKI: Yes. Kind of following up on that, you know, with the adventitious agents, you know, really kind of -- really looking more at an acute effect or acute toxicity or safety issue, where when I was looking at this part, you know, there is some of the materials that may be new or in the bioprocess that may be in there in small volumes and may not have an acute effect, but, you know, the way I look at it from a toxicology viewpoint, this may be more of a chronic exposure. So it may be low levels, you know, over a long period of time. So you need to do kind of, you know, more chronic safety testing versus an acute test, you know, for some of these materials that may be in there.

But, you know, looking at the background material, there is really -- you know, at least in the

near term, there is nothing there that, you know, uses a food additive now or, you know, a biodegradable substance. But, you know, as these things develop, you know, things like growth hormones over a long period of time or other things that are added to the media, you know, might have to have more chronic, you know, kind of studies to evaluate the safety.

DR. McLELLAN: Barbara?

DR. KOWALCYK: So just to follow up on that, I think that is one of my concerns, is that we don't understand what the impact is going to be in the long term. And it is important to remember that people eat multiple times a day. And it comes back to I think Rebecca's what does meaningful amount mean. It may not be a meaningful amount if you have a sporadic exposure, but it may be a meaningful amount if you have repeated exposure on a daily basis.

And, of course, one thing to consider as you try to grapple around this is thinking about the vulnerable populations. So children and the elderly are two populations that I think quite a bit about. They also tend to not have a lot of diet diversity. So

they tend to eat a specific product over and over and over again. And so whatever is in that product, they tend to get a higher dose, particularly children that have a smaller weight mass as well as the elderly can, too. So I think that those are important things to consider.

I do want to just come back from before the break, if I may, to the risk-communication point that was brought up because I think that was a very good one that is worth revisiting. First of all, I think that the agency needs to think, agencies need to think, very carefully about how to communicate risk. This product has already been put out in the marketplace with the label "Clean Meat." You know, that is why I have heard it talked about as clean meat. And it certainly implies that there is no risk. So when we get to the point of regulating this, you need to think about how will it be labeled.

I do want to say, just from my experience, that while most people do in theory accept the idea that there is zero risk, they do expect zero risk in food. And that is something that needs to be aware. I

mean, whether they should or not is a different story. You know, so this risk communication and risk perception is really critical for the agency to understand.

The other thing I want to come back to is the risks that -- we are talking a lot about what we have learned about through therapeutics. The risks that people who are sick are willing to take are very different than the risks that people who are healthy are willing to take. And so we are talking about primarily a healthy population and the risks that they are willing to take.

So I just want to -- I don't want to come off as overly negative, which I feel like I am, but I think that there are a lot of unknowns that we need to understand. And there does need to be a lot of risk-communication research that goes into this. And just keep in mind that you do have these different subpopulations that you need to understand. And we are talking about a healthy population. You know, what if kids were eating this every day, like they eat French fries or chicken nuggets?

DR. MAYNE: Can I just clarify two things? Thank you.

The first one is these products aren't in the marketplace yet. Maybe that was a misstatement. And there are no labels. So there is no product in the marketplace. There are no "Clean Meat" labels in the marketplace.

DR. KOWALCYK: No, no. I know there are none in the marketplace, but it is being referred to in the media as clean meat.

DR. MAYNE: Correct. And the agencies are aware of that issue. We have asked for a lot of public comment on it. We are going to have a whole-day session or at least part of a day session on labeling. So we are going to address some of those issues on Wednesday, on the labeling piece of it.

The other thing I think I should clarify on the zero risk, just from where I sit in my perspective, we know there are things like inorganic arsenic that occur naturally in soil. And so anything that comes out of the soil can have trace amounts of that. And with our ability to detect lower and lower and lower

amounts of any type of chemical contaminants, anything, as scientists we all know that there are going to be de minimis levels that can occur in foods. So if we say zero risk in the setting of increasing analytical precision, we know that is not accurate. So that is what I wanted to convey when I talked about zero risk. It is not just microbial but chemical, where we simply cannot achieve that based upon the world we live in.

DR. KOWALCYK: If I may -- and I fully appreciate that, and I think that that is why the risk-communication piece is so critical because how do you communicate that to the public that does have this perception of zero risk with food when they don't have it with other areas?

DR. McLELLAN: Okay. I have got Rodney. I will come back, Jeremiah, and then over here to Scott and Annalisa. Rod?

DR. BRISTER: Rodney Brister. So one of the things I kind of struggled with when I read through the materials is that we are not talking about one product. So there is a whole gamut of products at the most near-future look-like cell culture that is being used in

cell therapies but in the distant future look like something completely different. Right?

And so I would imagine there are two kind of -- at least there were two questions that came to my mind when I read this material. One is in the cell-culture environment, you are taking something that is a very thin layer, just a few cell layers deep. And you are post-processing. After you are growing it, you are processing it in some way. So one thing that would concern me perhaps is agents that are introduced or impurities that are introduced during the processing itself as well as the things that are introduced during the culture.

And the second sort of far-reaching idea, which is, you know, I don't think we are going to see steak come out of the processes that they are talking about now. I mean, if you want to grow a side of beef, you are talking about many different cell types. You are talking about, you know, essentially nutrient flow through those cell types and something very different. And the organization of it is very different. And perhaps the nutrients and the other products that are

made available for it to grow are different, both in terms of how much are there and how much is residual after you harvest, how much is residual in that, you know, side of beef.

So it seems to me from the FDA's standpoint, it is kind of difficult because you are starting at one place but you expect to be in another place down the road. And I am not sure how you internalize that in terms of your regulatory environment, but it seems to me a question that needs to stay in mind, that what you might be looking at today, it is probably an intermediate step to something else down the road.

DR. McLELLAN: All right. Jeremiah?

MR. FASANO: Thanks. It is just a couple quick points. The first one is just about exposure. So, as some of you probably already know, when we do ingredient safety assessment, we have a set of tools that we use to assess exposure, both for the general population, for individual subpopulations, because we are very -- we think a lot about exposure when we are doing safety assessment. Right? The dose makes the poison. Something that could be a concern at one level

is not going to be a concern at another level. And that is one of the reasons that this question focuses so much on meaningful amounts. Perhaps that wasn't the best choice of words, but the basic idea to get across here is, is this going to be present in food at levels that would actually have a plausible effect on the consumer versus levels that would be residual, would be detectable but would not be expected on the basis of our mechanistic understanding of the substances to have any effect on the consumer? I mean, that exposure, the level of exposure, is really important for safety assessment. It is not just whether something is there or not.

As Dr. Mayne mentioned, with increasing analytical ability sort of regulating by limited detection is not really possible anymore. And so what you are really looking at is at present levels, would there be a plausible concern for safety? Again, the standard is reasonable: the certainty of no harm in the minds of component scientists.

Another quick point is just in thinking about sort of the safety of a substance or of a food -- I

brought this up earlier, and this is also relevant in the context of this concept of zero risk -- consumers do understand, you know, about as safe as something else. Right? And so we have talked here about baselines.

The point of comparison may vary depending on which property of the food you are considering, whether it is a nutritional property, as you will get to in a minute, whether it is something having to do with microbial contamination, whether it is having something to do with residual amounts of various sort of growth factors and to what extent they are present in other foods we already consume. But that is a useful touchstone for analysis in general when we are thinking about substances. Particularly ones for where we are looking at low levels and trying to decide whether they are significant or not is what is the prior history of exposure to the substance or comparable substances.

DR. McLELLAN: Very good. Scott?

DR. STEELE: So Rodney really touched on my question, which was more of this post-harvesting or finishing or whatever the appropriate terminology and

what substances might be added at that point. And so does FDA have a sense of so far what that process looks like or what is being proposed by the industry?

MR. FASANO: I mean, I think the presumption without having a lot of actual working sort of manufacturing process to observe is that these would go into traditional food production processes after harvesting and there would be sort of comparable issues that you would typically experience in that setting. But I don't think there is a lot of practical --

DR. STEELE: Something really novel? Okay.

MR. FASANO: Yes.

DR. McLELLAN: So our second question -- and, Leah, maybe I will lean on you a little bit here to help me -- first, by talking us through the structural materials. And give us a sense of what at least state-of-the-art today might be and what is being explored for alternatives in terms of this scaffolding-type arrangement.

MS. STITZ: Currently items like collagen are used. And there is some use of microbead carriers, basically microbead, collagen set up in the stir tank

reactors to allow the adherence, yet suspension of the cells. Then that allows for greater volume production in those larger, more scaled-up quantities. The issue with that is once you have got them on those microbeads, you want to remove them from the microbeads and reuse the microbeads. Having not actually done that myself, I can't speak to it very much, but I do know that that is one sort of scaffolding used currently for the more comminuted meat, hamburger-type products, sausage-type products.

Additionally, looking at plant-based, I have literally seen devascularized vegetables, you know, lettuce leaves and things like that, as potential scaffolding materials. One of the papers in your background reading was talking about an edible scaffold made out of fish gelatin and alginates and things like that, additionally talking about using various structures through 3D printing as scaffolding materials. So a lot of research is going into this.

And, as I mentioned, it kind of depends. Is your scaffolding going to be more like a bone or is your scaffolding going to be something more like

connective tissue? Additionally, is your scaffolding something that is going to continue to persist with the product or is it something that is going to degenerate over the production of the product and essentially become invisible or absorbed by the cells?

Does that basically answer your question?

DR. McLELLAN: Go ahead, Lynn.

DR. GOLDMAN: Yes. So I was gathering, you know, in the reading that some of the scaffolding materials might be material like collagen, perhaps collagen beads. Forgive my ignorance, but is there recombinant collagen? Can you make that in a lab or is that going to come from an animal? What would be the source of that kind of material would be the question.

And then I also could see that some of them might be synthetic materials that are hopefully kind of, you know, biodegradable or inert, but I was just -- you know, what do we actually know about the materials and where they are sourced, the ones at least that people are experimenting with now?

MS. STITZ: The collagen can be recombinantly produced.

DR. GOLDMAN: It can be.

MS. STITZ: And that is a predominant scaffolding material at this time. Like I said, there is a lot of research. Hydrogels are especially promising, but right now the primary scaffolding structure is various forms and formats of collagen.

DR. GOLDMAN: Okay. Can you give us an example of a hydrogel? What are those chemically, hydrogels?

MS. STITZ: Hydrogels are basically -- remember those water crystals that you could buy and put in the soil for your plant and you add water and they hold water?

DR. GOLDMAN: Sure.

MS. STITZ: Okay. That is the most recognizable consumer product of a hydrogel. So those types of products could potentially be used as scaffolding materials, in part because they allow the absorption of water and they allow the adherence of cells. But they would have to be hydrogels that are either removable or consumable.

DR. GOLDMAN: Thank you.

DR. McLELLAN: Thank you. Jeremiah, is your flag up?

MR. FASANO: No. Sorry.

DR. McLELLAN: If not, we will go to Sean. Thank you.

DR. XIE: Leah, I have a question about those biodegradable materials or the hydrogel you are using. Based on the experience we have, sometimes we -- we did a study trying to use polymetric material holding the drug for release. And we found out in the end, it was always holding some of those things in it. So what we did to the first question, when you put in those growth hormones, the small molecule or chemokines, so at the end of production, maybe it is difficult to remove. So I don’t know any regulation on what kind of scaffold should be recommended to use or not use.

MS. STITZ: I don’t think we are at a point of regulating --

DR. XIE: Okay.

MS. STITZ: -- necessarily what they can and cannot use as scaffolding materials until we have some additional input from industry on what is working.

Obviously industry has a need to keep their research proprietary. And there is a limited amount of information on exactly what scaffolding materials are working and what molecules, if any, are adhering to those scaffolding materials.

DR. XIE: So assuming at the end of the production, harvesting, they are going to purify or wash out those residual small molecules, other add-ons, how do they do the final --

MS. STITZ: Have you got an answer for that one?

MR. FASANO: Yes. This is Jeremiah. I think that, you know, this may be a useful way to think about this as sort of going back to a concept I had introduced earlier about it being reasonable, serving no harm for the intended use. So if the intended use of your structure, particularly if you have got some kind of scaffolding material that has also got, you know, chemokines or other sort of things to help with differentiation on them, the intended use would involve that. So if you were going to be doing a safety assessment, particularly for something that was

remaining in the food, it is a food ingredient, then that would also incorporate sort of any modifications that were made to it for that use.

So, I mean, it is very specific to the intended use, not just the chemical entity itself but what is the structure, how is it being used, what is the exposure. All of that would sort of factor in. So I think as a general thing, we could say that, you know, safety assessments for substances added to food are always about how are you using it, how much exposure is happening, and sort of what is the substance actually going to look like at the point of consumption because that is obviously the relevant thin for safety.

DR. McLELLAN: Okay. Yes? Go ahead, Lynn.

DR. GOLDMAN: So, you know, a thought on this. And I wish, you know, I had something more specific to say, but, I mean, I am actually now doing a little bit of reading. And I realized there -- so some things we are very familiar with, like -- actually, gelatin and collegian are also considered to be hydrogels. So they are not all synthetic. And so I

think some of them would end up being materials that already regulate in the food supply and may even be in like graphs.

You know, that doesn't mean that everybody likes some gelatin. It is not a vegetable product, for example, nor is collagen unless it is made recombinantly. So that is a little weird. But there are some that are synthetic that are where they are made, you know, with monomeric chemicals that are polymerized. And you might go to EPA about those. They actually have, what I am seeing, a lot of industrial uses other than potentially being used as scaffolding. And there may be data they wouldn't have necessarily paid much attention to given the industrial use that would be important from the standpoint of having it in the food supply. So I think that that could be worthwhile.

Oftentimes with some of these polymeric substances, just like everything else, there are little added things, added ingredients, that are necessary to their functioning to act the way they want them to act. And EPA is likely to know about that kind of thing. So

I think that might be a good place to just start, you know, understanding what some of these are. We might be able to learn things that even industry doesn't know because some of them may be protected, you know, under CBI if it is really, you know, the trade secret on stuff.

DR. McLELLAN: Okay. Let's go on to our next set of questions. And again I will turn to our external experts to start this conversation. So our first question being asked is, what is the likelihood that that cultured cells could produce harmful substances in errors in the culture process?

So would one of three of you like to? Thank you, Rebecca.

DR. SHEETS: I wanted to give you an opportunity to start.

This is Rebecca Sheets. So, I guess, rather than errors in the culture process, I would think of it more in terms of if a culture process weren't optimal or if it was not an optimized process, then certainly you can begin to see the cells die. Even during normal culture with robust growth, some of the cells are going

to die. And, of course, the cells die. They do produce things like tumor necrosis factor and proteins that facilitate the cell death process. And so whether that would be harmful or not, I mean, I see it as if you didn't have an optimal process and you had a massive amount of cell death, you wouldn't be able to produce a product. Right? So you would probably end up with something that was not harvestable. You wouldn't get enough out of the culture to produce your lot of meat.

And if you only had a minor amount of cell death, then I think, you know, that is probably not unlike harvesting meat. You know, from the moment it comes out of the animal, the tissue is dying and dead. And so it is just a matter of how rapidly the cells are degenerating and what percentage is degenerating. I think you can keep monitoring viability, et cetera, et cetera, and have quality control standards that would allow you to monitor for those processes and say, you know, if it is too much, it is not acceptable or it is not of suitable quality. So I don't know if that is a helpful comment.

DR. McLELLAN: I wonder if it was less about the senescence of the tissue of the cells and more about literally the cultural process and the growth process. I think that was really where this question was more poignantly aimed.

DR. SHEETS: Well, of course, you are going to get waste from any growth process. And so part of what you do in cell culture is depending on whether you do a bad batch process or you do profusion culture. If it is profusion, you are constantly taking the waste away and putting fresh culture media on. So it would depend on how the culture process is done whether you are going to get an accumulation of these waste products.

Is that what the question is driving at?

DR. McLELLAN: It could be that or it could be pointing at a potential direct result of the growth of the cells.

DR. SHEETS: Right. I mean, if the cells start to grow uncontrollably and de-differentiate, then, you know, you might get the production of ankA proteins that are driving uncontrolled cell growth.

And in that case, again, I think you would have quality control measures that would detect something like that going on, but you would also -- you know, you are producing proteins that would be digestible. So I am not sure that I am helping you identify a risk there.

DR. McLELLAN: Rodney?

DR. BRISTER: Rodney Brister. This is a question I actually had, too, when I was reading the materials because, you know, it depends on how you do it, right, and if you have immortalized cell lines or if you are, you know, making primary cell lines and asking to transform the cell, as you can imagine different inherent risks. I mean, maybe some of the people on the other side of the table can speak better to this. The one thing I see -- and I think Becca was just kind of hitting on it -- is that if you are growing cells in order to express something, large quantities, and then purifying that something away from the cells almost exclusively, you have kind of lowered any risk that was associated in growing those cells, any factors they may excrete. And the risk to the human is minimal.

But then if you are in a situation where you are going to harvest those cells and those factors may be sticking to the cells. They may be, either indirectly or directly. And you may be harvesting those factors alongside those cells. Do you create some new risk that, you know, maybe it was always seen as a very minor risk? And I don't really know the answer to that question, but I think that is probably what you were getting at. And so in the transformation process, yes, you have changes in transcription. Does that impact endogenous viruses or does that make this all secrete things that could be harmful to humans?

DR. McLELLAN: Annalisa?

MS. JENKINS: I can't resist. Annalisa Jenkins. I am not sure I can answer this question. And the reason is that there exists today a lot of scientific debate amongst those that have been working in the production of cells as therapeutics over many years as to the best way to produce pure cells of a lineage that is sustainable and safe, et cetera. The reason that I bring that up is just really to say that there is a lot of debate about this, actually, the

starting material, how the cells are produced, how they are differentiated and stabilized, and, therefore, how to think through the sustainable quality of the final product.

And so I guess my only suggestion is that it will be really useful to bring together that group of scientists that have spent their lives working on this and debating this topic because I think that some of their understanding of this question might be very, very useful. And they sit across, you know, both the regulatory side but also the commercial side and academic side as well and the fact that there does exist so much debate today in this space I think points to the fact this was quite a lot of science that is still evolving an understanding.

DR. McLELLAN: Sean?

DR. XIE: I have a quick question since we are talking about the cell source. So in the morning, Cindy was talking about there was a different choice: master cell.

And also somebody mentioned they could use a stem cell. So would we be using embryo stem cell,

adult stem cell, or just a regular animal muscle master cell? What is the advantage among those different cell sources? And what would be the impact later? Any risks associated?

MR. FASANO: I mean, to take a first stab at that, I think in general, without, again, having scaled industrial levels, the more flexible the cell, the more sort of effective the proliferation is going to be and probably the better yield you are going to get there. And so the extent that you can do sort of induced pluripotency -- and there is a variety of techniques for that now -- regardless of your starting material and get closer to a de-differentiated cell for the proliferation step, I think that is likely to be desirable from an economic or industrial sense.

In terms of risks from those different sources, I mean, if I could just kind of clarify, the thing we sort of touched on we were thinking about here is in culture processes, certainly for plant cells and for fungal cells but also for some microbial cells. If the cells are under stress, they tend to make a lot of protective substances that can also be toxic. And

certainly making toxic substances is more of a go-to strategy for plants than for animals, but, you know, it does sometimes happen.

And so we just wanted to throw out there whether folks had a sense of what kinds of substances, particularly under sort of stressful or non-optimal culture conditions, might be of potential concern, again, calibrating against potential exposure in the final food. But that was sort of the origination of that question is our experiences with cultured cells from other kingdoms.

MS. JENKINS: Mark, can I just go?

DR. McLELLAN: Yes, absolutely.

MS. JENKINS: Because I probably wasn't so clear --

DR. McLELLAN: Go ahead.

MS. JENKINS: -- in my previous comments. And it was actually related to just what you said, that I am not an expert in understanding what those chemicals might be, but I have been part of a number of forums recently talking about the difference between the basic induced pluripotent approach versus the

missing chimera approach and the relative benefits and risks as it relates to the topic that you are addressing here. So that was the point I was making, that I am aware of groups that have been thinking very actively about that question and working that through in a different context. But it will get to the substances that they are already thinking about and addressing.

MR. FASANO: So if I could just ask a clarifying question. So you are saying that there seems to be some question about the kinds of potentially harmful substances that are produced from those two different sources or cells?

MS. JENKINS: That is correct.

MR. FASANO: And what kinds of substances? Do you have a sense of what kinds of substances those are?

MS. JENKINS: I do, but I can address that offline with you and --

MR. FASANO: Okay.

MS. JENKINS: -- referring you to the experts, but that was the point I was making, that

there are different views on the relative risks as it relates to the two different platforms. And it gets to the question I think that you are asking.

DR. McLELLAN: Sean, I think your flag is up. It is not up. Okay. Go ahead, Lynn.

DR. GOLDMAN: But it seems like at that point, it is not about, really, an error in the process. It is the choice, the choice of the cells to use as a base, right? And I think that that is very important because you are talking about cells that are coming from different points in developmental trajectory and because of that may be programmed to do different things biologically. And so it is not the same thing as an error, but it is something that needs to be I think thought through carefully because those cells may be programmed to do things other than simply differentiate into muscle. They might be programmed to do other things: signal each other and things like that.

DR. McLELLAN: Rodney, go ahead.

DR. BRISTER: Rodney Brister. And that kind of goes to my point it keeps coming back to that,

really, you are talking about what are the specifics of how one group is producing one product. And, you know, if you have multiple cell types in there, by design, are the risks different because of the way the cell types interact with one another or, maybe more to the point that was just made, that you may in that what you think is one cell type, actually, have a small population of cells, right? And it really gets down to the sort of granularity of what is this group trying to do in order to make their product.

DR. McLELLAN: Indeed. It also comes core to the question, do you start with a presumption that it is food and intrinsically safe to a natural extent?

Without further -- go ahead, Jeremiah.

MR. FASANO: That reminds me. I just wanted to sort of bring up a point there in terms of that presumption. I think maybe a piece of that difference in approach really relates to an inference that you can make from the intended use of the substance, right? So a drug is intended to derange, often quite dramatically, the physiology of the person consuming it. Food generally is not. And so that gives you a

different sort of parameter space to think about in terms of your probability of risk.

And so in this case, these foods are being produced using methods that are used to produce biologics, but their intent is not to produce dramatic derangement of the consumers' physiology. And so that may also influence sort of your starting exploration space for thinking about risks.

DR. McLELLAN: Great point.

DR. SHEETS: If I might just get to that? I mean, I come from a perspective of vaccines that we are giving mostly to healthy babies and that while they are immunogenic, you know, we don't want them to be toxic at all. And we certainly don't want them to have long-term consequences other than to prevent the disease they are intended to prevent. However, they are only given a handful of times. They are not eaten every day. You know, they are not three times a day every day. They are not chicken nuggets.

DR. MAYNE: And the other complexity -- I will just jump in here -- is on these harmful substances. You know, obviously they may be affected

by heat treatments, cooking, you know, which may be, again, different than the biologics. And they may be orally ingested and digested. So if they are protein-based, that is a whole other set of scenarios. So there are certainly parallels with the biologics but obviously some key differences that we have to think about as we think about the safety and what we need to be aware from a preventive controls framework.

DR. McLELLAN: Go ahead, Lynn.

DR. GOLDMAN: Another point, then. I was just wondering if it has been considered at all. And that is the people involved in the production of these. So I know so little about how cell culture works and especially in a large framework. I am guessing that ammonia is a waste product and some other nitrogen-containing compounds. And so at least to consider whether toxic nitrogen products could wind up off-gassing, especially if there is a batch that goes bad. And, you know, we are not just thinking about the consumers of the food but also the people who work in the places that they are made or the people who work with the food as potentially being harmed if you have

got accidents that occur.

DR. MAYNE: I guess I will take that one. You know, our concern is obviously the food safety piece. That would be an OSHA issue. Occupational Safety and Health would be concerned about the health of any workers. But any information that you could shed light on, the processes, you know, any potential hazards, that would be something we would certainly be willing to share with other Federal agencies as we are learning about these products.

DR. McLELLAN: Barb?

DR. KOWALCYK: Barbara Kowalcyk. As we wind down, Mark, I was just wondering. I looked back at the questions that we have been asked. And I don't know. I guess my question is, have we adequately answered the first question in the second set in that, are ordinary food ingredient evaluation procedures sufficient to ensure food safety? Did you get the answers that you were seeking to that question because I am not sure we directly answered that?

MR. FASANO: I mean, I guess one of the things we were hoping we might hear is a discussion of

-- and it may be that this was, you know, too ambitious to try to cover in this context, but a discussion of the classes of substances, which we covered that a little bit, some of their properties or predicted effects that might be of concern for human consumers, and then maybe a discussion of sort of the exposure levels at which those, you know, effects might manifest because that is really the kind of information that we would want to consider if we were thinking about safety. And that kind of gets to the meaningfulness.

So we didn't really get into depth in any of that stuff. We touched on sort of some broad classes of stuff, but, you know, again, given the time, perhaps it was too deep in the weeds.

DR. McLELLAN: Go ahead, Annalisa.

MS. JENKINS: I guess as I was coming to this board, I was feeling wholly inadequate perhaps to get into the level of detail that you perhaps anticipated, largely because I guess one of my opening comments was that this field of cell culture is complex. It tends to reside in certain groups, I think, that have a lot of knowledge. And I guess one of the messages that I

came with today was that there is a lot of knowledge out there. We have seen that today. But it also exists in pockets of people that have spent years working in this space and I believe that have never felt that their skill sets and knowledge might be imparted in this setting. So now it is our job to help connect you to people I think who will actually have the answers to those questions or at least start the debate or have a perspective on them.

DR. McLELLAN: I also think it was Rodney who said where we start is probably not where we will end up with this whole game. In other words, you know, we are at the very early stages but absolutely worth plugging into others that have knowledge.

So, without any further questions, let's go on to the last one, which talks more about the nutrient value and differences we may see. So again I will reach over here. And maybe, Rebecca, you can kick us off here with a commentary.

DR. SHEETS: I am not a nutritionist. So I am afraid this question for sure is not one that I can answer. I mean, on the face of it, I don't see why it

would be different, but I would -- I am not an expert on nutrition, as you can tell by the fact that I desperately need to lose weight. I am over-nutrienteD.

DR. McLELLAN: Well, we are fortunate to have a nutritionist with us. So, Connie, we can push you. Jump in.

DR. WEAVER: Yes. Thank you.

So I can think of several ways it might differ. For example, the iron content of different muscle types depends on the myoglobin concentration, which is responding to exercise. So dark meat is the exercised muscles. I don't see any exercise in tissue cultures. So is it all white meat? I don't see. I could see the iron content being lower. Copper comes from connective tissue. So if you don't have that cell type along, you could have a different copper level. I am thinking about the nutrients that we depend on for recommending protein sources in the dietary guidelines. And those trace minerals, along with zinc, are the ones and the micronutrients, protein and amino acids, of course. It is a high-quality protein. And that is very important. In America, we don't tend to be scarce

in our protein intake, but the quality of protein is generally superior from animal sources, then, plant-based sources. So we certainly need to be mindful of any replacements. That I am guessing would be similar, have to be confirmed; whereas, these trace elements that are dependent on cell types and in response to exercise and so forth, that can be different.

DR. McLELLAN: Cynthia?

DR. AFSHARI: I don't have a comment in terms of what we might lose or in terms of the beneficial things, but one of the things that I am thinking about, you know, for example, fish and mercury. And so as you think about if this were to be successful, it may be a way if you are controlling your water and other things where you may introduce impurities, you may actually introduce some positive aspects in terms of eliminating some concerning things that are in our diet now.

DR. McLELLAN: Leah?

MS. STITZ: I apologize. I apparently left part of my description out in my overview today. I meant to tell you that one of the things that the cells require is exercise. And part of the reason for the

scaffolding material is to allow for potentially mechanically stretching the cells and/or using electric current to stimulate the cells and cause contraction. So these are ways that the cells would be exercised. And exercise is necessary for these cells in order to have a proper texture for the finished product and to make sure that they have the right protein content.

DR. WEAVER: But does it get into white meat or all the way to dark meat?

MS. STITZ: I haven't been told that part yet, and my reading on that was not clear.

DR. MAYNE: Yes. But, Connie, a question I would have, then, is if it is not there through the myoglobin or through some other way, can it be added in in some other form to get it into the cells, like the nutritional inputs? Are there other ways to get those nutrients into the cells so you could achieve a similar level of iron or copper or whatever that may be?

If we are thinking about, you know, the fish sources, the seafood sources, you know, what are the levels of Omega 3's that you could put into the culture? And how would that affect the finished

product because we know in our natural seafood species, there is enormous variation in the amount of Omega 3's. You know, what kinds of effects might that have on membranes? They are highly polyunsaturated. So could you achieve higher than, you know, typical nutritional levels of Omega 3's or would that affect membrane rancidification or something to that effect? So those are the kinds of questions I think we would love to hear more information on.

DR. WEAVER: And closer to your background, what about vitamin D? Because when the vitamin D recommendations came out in 2010, one of the very curious things is how is it that Americans are consuming so much less than the recommendations, but their status, 25-hydroxy D, is adequate. And then subsequently more testing was done on animal products to show there is 25-hydroxy D in these animal products. We may lose that unless we are mindful of adding it because apparently that is making up the gap for adequacy.

DR. McLELLAN: Tony and then Rodney.

DR. BAHINSKI: So I am really fascinated by

the comment you made about the mechanical and the electrical stimulation because I think you are right on there. You know, the bioreactors are often for kind of epithelial cell lines that are kind of amorphous. And, you know, muscle, skeletal muscle, cardiac muscle, is highly structured and anti-psychotropic. And so, you know, there is lots of studies in the literatures where, you know, in these in vitro laboratories and organs-on-chip systems that are being developed. You need to micro pattern or, you know, get that organization, either by mechanical stretch or stimulation to get the proper orientation of the contractile protein.

So just, you know, whether it is white or dark, it is probably lacking, you know, a lot of the density of the proteins in there because contractile proteins are extremely sensitive. So the scaffolds are going to be exclusively important in that, whether they can actually mechanically stretch because often in these systems, the organs-on-chip systems, they are using the same growth factors, same media. The only difference is the biomechanical stimulation. And that

profoundly changes the phenotype, profoundly changes the phenotype as well as the transcriptome. So I think that is a really, really interesting comment.

DR. McLELLAN: Rodney?

DR. BRISTER: Yes. One thing that the question struck is, what exactly is the product space? So if you are marketing something as meat, should it be compared to meat? And I think this goes back to everything we have talked about, like what are the acceptable risks? And to what should we be looking for? But also what are the nutritional components, right? And in going back to my earlier point that we are in early stages, so is it still meat if I take five or six components and combine them, that are grown separately or made separately somehow and combine them, together, which I think was at the heart of what you guys were saying or is it only meat if all of these pieces are put together, you know, together in one and growing experience, which I think is still a little bit sci-fi?

Then the other thing is, is there a difference between fish and meat? So if I market

something as fish, you know, it has natural properties that some see as health benefits. And it may be attractive to the consumer, but are there going to be separate guidelines for establishing what the rules are for fish substitutes versus beef substitutes versus chicken substitutes?

And then kind of rocked into this, the thing you just hit on really struck me last night when I was reading and thinking about things, that, you know, right now -- I don't know. I can't remember where it was. Many thousands of liters to grow two kilograms of steak says to me the density of what is being grown there is not anywhere close to the natural density. So that is on this sort of population level of cells. What is going on in the cells? Are they as dense with muscle fibers? Do they have all of the protein components and other components? I think there is a big question that can be easily answered about the nutritional value of what is coming out of these cultures, right? And there is a secondary question as to what the target needs to be in order for you to market it as something.

DR. McLELLAN: Okay. Lynn?

DR. GOLDMAN: Yes. I have I think a couple of comments on that. I mean, one is certainly that -- and I know you guys know this very well, but it is not just the composition of the product but also how it is packaged. That can be important. Like with iron, some forms are absorbed a lot better than just elemental iron isn't that well absorbed, right? So just tossing in iron isn't going to make up the difference if you don't have as much that is being formed, as has been pointed out.

On the other hand, there could be some things maybe that could be omitted. I mean, you know, so meat people want meat to have a sensory feel that there is fat in it. But the fat that is naturally in meat, we don't seem to think it is the best fat, you know, for people to be eating. So maybe there is a potential actually to form this in a way that, you know, you are not manufacturing the fat cells at the same time as the muscle cells. But maybe there is a source of fat that is from a different animal. Maybe you are mixing fish and beef, you know, and you are getting Omega 3's with

your hamburger. I don't know. That could be a good thing. I mean, it sounds a little creepy, but that could actually, you know, be an improvement, you know, over meat. So that there are some opportunities there as well if there is a way to do that and a way that, you know, tastes good. I don't know. I don't know how that would taste. But I think there has to be a lot of care in terms of not relying just on composition, but I know you know that.

And I know that FDA looks a lot at whole animal feeding studies and things like that. You might need to go to that if you have got something that has got a lot of artificial components.

DR. WEAVER: So what is the role of the gut microbiome in the traditional animal in supplying nutrients or health-promoting byproducts that could be missed here?

DR. McLELLAN: Interesting. Interesting. Tony?

DR. GOLDMAN: Is that microbiome of the cow you mean?

DR. WEAVER: Yes.

DR. GOLDMAN: Yes.

DR. McLELLAN: Jump in here, Tony.

DR. BAHINSKI: So maybe going down a rabbit hole but I think following up on, you know, kind of identification, so there were some interesting comments. I forget which paper in the background reading that was talking about developing protein markers in aspects of, you know, giving the tools to the inspectors for product verification. A little bit aside, for one is, you know, nutritional value, you know, identifying, you know, what different components are in there, but also I thought it was interesting they mentioned food fraud, so basically, you know, verifying that people weren't saying cultured meat and it was actually conventional meet or vice versa, conventional meat was actually -- depending I guess which one is cheaper to develop.

So is the FDA developing -- are there kind of, you know, protein markers being developed out there that can identify if a particular end-processed meat is from a conventional versus a cultured meat?

MR. FASANO: I think that there are

definitely markers that can tell you if particular cell types are present, right? You just, you know, look for ones that are associated, particularly differentiated and say I am not aware of anybody doing work trying to sort of think about, you know, presenting one as the other. I mean, just, you know, it might be tricky because, you know, if you are running the process appropriately, you are going to get at least some of the same cell markers.

DR. BAHINSKI: Right.

MR. FASANO: So just thinking about the logistics of that seems kind of tricky.

DR. BAHINSKI: I was just wondering.

DR. MAYNE: Yes. I can tell what we have done in the traditional space. It is best probably in the seafood space where there has been an issue, as you know, with seafood fraud. So CFSAN developed DNA barcoding methodologies to rapidly look at it, but it is based upon genetic diversity across different seafood species and having a library of those genomes that you can then use a quick methodology to do barcoding. So we have done that in the conventional

space, but, like Jeremiah, I am not aware of anything that has looked at that. That would be presuming that there would be genetic differences that you could identify with some type of a marker.

DR. BAHINSKI: Yes. There might be ways to genetically put those types of barcodes, but, then again, you get to the issue of you are genetically modifying the food. So you might want to stay away from that. Yes.

DR. McLELLAN: Leah, did you have a follow-on?

MS. STITZ: I apologize. This is Leah Stitz. And I wanted to comment on what Rodney had brought up about, can there be meat if not all cell types are present? That will be part of the discussion again on Wednesday at the joint USDA-FDA meeting, but I did want to remind you that, you know, some firms are also looking at and working on co-culturing of multiple cell types into 3D structures to -- one company in Europe is -- I mean, that is their solid-stated goal. They are coming out with steak. That is their intention. They are going to have a 3D structured meat that looks like

steak. They are not planning to work on anything else, any intermediate steps. That is where they are going.

And other firms are looking at -- rather than co-culturing models, instead, they are doing the cells separately, then combining them using 3D printing. So, again, there are multiple ways to get to that 3D dense cellular structure that we anticipate a meat product being like.

DR. McLELLAN: I know a rancher that would have a hard time with that.

Let’s go down here to Sean.

DR. XIE: It is a very exciting field in a lot of those things, those cell culture meats or biosynthetic meat. So I will have to come back to the nutrition point. During the processing, we can introduce all kinds of stuff, as you mentioned, Omega 3 or others, but at the endpoint where all funneling to the end, you have how we access those nutrients. Are we going to use animal tests, testing feed back to the animal to see how good, or are we going to be using like public trial? How do we access nutrients at the end?

MR. FASANO: I mean, just in terms of bioavailability, that is something we routinely consider, particularly when we are looking at various things that are sort of fortifying of food, right, obviously different kinds of chemical forms of the same nutrient, maybe more or less bioavailable. I mean, I would characterize that as sort of a routine part of looking at ingredient assessment, thinking about the bioavailability.

DR. XIE: So we would go back to is in vivo animal or human bioavailability?

MR. FASANO: Well, there is often quite a lot of data already about different forms, like, say, you know, an inorganic versus an organic form or, you know, different chelates. I mean, that sort of stuff is -- there is a lot of information already out there. I think that you probably in many cases could make inferences about bioavailability without even additional animal data.

Did you want to add anything to that, Dr. Mayne? No? Okay.

DR. McLELLAN: Okay. Connie, if you would

just pause for a second? Let me just check on the line on the phones. Do we have anybody still with us who would like to ask a question?

[No response.]

DR. McLELLAN: Okay. Hearing none, let's go ahead. Connie, thank you.

DR. WEAVER: Okay. So maybe to start with some overarching guidance from what we have been gathering today, so two things that come to my mind are I think this may require more rigorous post-marketing monitoring than for traditional foods because so many uncertainties that we heard about today.

And the other piece of guidance that I would suggest is make it easy for companies to communicate and do the right thing for problems they are running into, rather than so limiting that they are afraid to tell you.

DR. McLELLAN: Okay. Barbara?

DR. KOWALCYK: So I just actually wanted to follow up on something Connie had said earlier in terms of the gut microbiome but not thinking about the animal gut microbiome but thinking about the human gut

microbiome, which we now know the gut microbiome plays a huge role in our immune system and our immune response and how will these new products potentially affect the microbiome.

And also from a nutritional perspective, you know, what we eat can also impede or promote our ability to absorb nutrients. So when you think about the scaffolding -- and I have to admit I am not a laboratorian. And I know enough about those things to be dangerous basically, what I read yesterday. But as we think about this type of scaffolding and culture materials that we are going to allow, realize that those may end up in our guts and may actually impede or impact that.

In terms of overarching thoughts since Connie opened the door on that, I mean, from my perspective, if we could achieve what people want to achieve -- and that is environmentally friendly, sustainable food sources that provide good, adequate, safe nutrition, I am all for that. But I am struck by the level of uncertainty that there is.

And so, coming back to the question that I

mentioned earlier, given that level of uncertainty, at this point, I am not sure that the typical food ingredient evaluation procedures that we have in place in this country are sufficient to ensure food safety at this time. Hopefully we will get to the point where we would have enough science that it could, but I think that there is a high level of uncertainty that raises doubts in my mind about that.

DR. McLELLAN: Rodney?

DR. BRISTER: Just two quick comments. I am aware of studies in the agricultural realm where they are looking at the impact of feed on the gut microbiome of cattle. So, I mean, that is a perfectly great idea, I think.

And then, to Connie’s point earlier, it seems to me this is because of your early days in the technology, this is a great place for the FDA to form partnerships with the companies developing these things so that you are, again, not -- the companies are not afraid to admit mistakes or to show, you know, their problems. And they can be discussed openly in a frank way that leads to a regulatory framework that benefits

both the companies, the consumers, and the regulators themselves. So I think that is a very good point.

DR. McLELLAN: This is a good time to pick up some overarching comments if you would like to add them before we close out. Go ahead, Laura.

DR. TOSI: I just want to go back to a comment from much earlier about risk. I thought I would be young forever, but I am not going to be. And I am fascinated as someone who has significant toxic exposure in the operating room by the development of allergy to God knows what that exists in the OR. I can no longer wear typical OR gloves. I am not allergic to latex. I am allergic to the accelerant that holds the latex together.

Listening to this discussion, I think that the accumulation of very small amounts of potential toxin is a message that has been coming out throughout the day and is very concerning if you imagine a world where one converts to this foodstuff because you can feed or potentially feed so many people at such a potentially lower price and then 10, 20, 30 years later, people can’t use the food anymore.

I think we have talked about post-marketing surveillance on and on again, but I think there is a lot to this. I am a very expensive surgeon simply because of what I have to wear, not what I charge. Just a little thought.

DR. McLELLAN: David?

MR. REJESKI: Yes. Just a few overarching comments. I think we keep coming back to this issue of scale. I just did some quick numbers. I mean, to displace or to substitute 10 percent of the overall beef production right now, we would have to produce six and a half megatons of meat. And we are talking about kilograms.

So I think there are a bunch of risks that we have to be aware of that are structural in nature. The first one is our scaling risks. And we start to go to scale, and we start to move from lab to industrial production processes. Things change radically. And we are going to have to figure out how to do that. And it is going to be a constant evolution or revolution in terms of how we actually go from gram to kilograms to kilotons to gigatons because that is what we need to

do. I mean, we shouldn't deceive ourselves so we can produce a few kilograms and solve any of these problems.

The other one you have to keep in mind is the spatial distribution of production. I mean, Connie brought this up. What happens if the people who want the meat are not here? They are not in countries that have kind of administrative oversight. They might be in China. They might be in India. So there may be demands for this kind of process that are in areas that don't have this kind of scientific capacity.

And the third thing is there will be new entrants into this area that are nontraditional. The fact that I can buy G netting machines now for $170 on Indiegogo means the whole price of entry to play in the biotech space means that there is a bunch of nontraditional actors that will come into this space.

So these are sort of structurally related risks that we have to be aware of that go beyond just the kinds of things we have been talking about, but I think as we go forward and we try to scale to gigatons or whatever we have to produce and it is literally in

the megaton-gigaton range, we are going to have to deal with how do we produce, where, who is involved, what kind of oversight do they have? And I think that is a discussion we can start having, actually, now just in terms of the scenarios, the production scenarios.

DR. McLELLAN: Okay. Barb, one --

DR. KOWALCYK: Sorry. Just made me think. One of the points that I wanted to make -- and we have had this conversation today, and we have had it at I think every Science Board meeting that I have been at -- is in terms of resources and do you have the scientific capacity within the agencies to conduct the research needed to achieve the agency's mission.

I think, again, one of the things that we are going to -- moving in this direction will make that even more critical because I am concerned about the resources and capacity that the agencies have to already meet the mandates, the food safety mandates, that they have. And then you add layer this on top of it. Both for FDA and USDA, it is going to require more resources. And I would hope that you would communicate that to your management and the powers that be that you

are already strapped thin in terms of both financial and human and scientific resources. And to move this forward is really going to require more investment.

DR. McLELLAN: Tony, one last comment?

DR. BAHINSKI: You know, listening to all of the arguments today, I am really kind of struck by the magnitude of the task at hand, especially with, you know, the scale. And it is not a new idea. So in 1931, Winston Churchill wrote an essay where he predicted synthetic meat production. And, you know, to paraphrase him, it was basically, you know, think of the absurdity now, you know, wanting a chicken wing or a leg and having to produce a whole chicken to get that. So, you know, that was, you know, entitled, "Fifty Years Hence." And so here we are 30 years beyond that. And I think we are just starting to have the technology in place to really, you know, get some traction around this.

So I am encouraged. I think there are some, you know, real key issues here that need to be solved in how to regulate this. But it is a tough issue.

DR. McLELLAN: Very last comment, Lynn.

DR. GOLDMAN: Well, I think it is going to happen faster than we can imagine. I am just thinking within my own lifetime when I was at EPA a long time and we were first looking at a few little spindly plants that some of the companies were growing that were, you know, genetically engineered and recombinant plants. And it took them forever to grow them up. And you kind of had this picture it would be years and years and years before they would even go on the market. And, you know, boom, they took over the market within five years of that. And there were millions of acres planted with them in this country. And it sure didn't look like that was what was going to happen. It just didn't look that way at all. So I think it is smart to be ready.

And I think one thing that might be really worth thinking about there is, you know, the regulatory science collaboration between FDA and the NIH, which has largely in the past focused more on drugs and devices and medical things, but I think that some of the issues that are involved in this space with particularly some of the substances that may be used to

pump up these cells to get them to grow at high volumes as well as some of the substances that some of these cells, especially if they are more stem cell-derived or even that might be elaborating, actually elaborating, that there are important things to learn, not only in terms of the safety of the food but also within other areas in health, such as cancer therapeutics, cancer prevention, other chronic diseases that could be impacted by these, that there could be a lot of interest by the NIH in collaborating with you.

And it might be a way to bring in some resources for the research that you need that could possibly go beyond what the FDA actually has or certainly that, unfortunately -- I mean, I wish. I wish it were more, you know, in CFSAN but that CFSAN has. I think this could be worth exploring, this kind of collaboration.

DR. McLELLAN: Okay. Thank you very much.

We are ready now to conduct our open public hearing portion of today's meeting. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and

decision-making. To ensure such transparency at the open public hearing session of the Science Board meeting, FDA believes it is important to understand the context of an individual's presentation. And, for that reason, we encourage speakers at the beginning of their oral statements to advise the committee of any financial relationship you may have with the company or group that may be affected by the topics of today's meeting. If you choose not to address this issue of financial relationship at the beginning of your statement, it won't preclude you from speaking.

And I understand that we have four requests. So we will proceed down that list, starting with New Harvest and Isha Datar.

MS. DATAR: Hello.

DR. McLELLAN: And, as I indicated, we have 10 minutes.

MS. DATAR: Yes.

DR. McLELLAN: I will give you a signal on two minutes.

MS. DATAR: Great.

DR. McLELLAN: And then we will close out.

MS. DATAR: Thank you.

OPEN PUBLIC HEARING

MS. DATAR: So I work at New Harvest, but I don’t have any financial conflicts of interest.

So thank you to the -- sorry. I am starting again. Thank you to the U.S. FDA for convening this milestone meeting and to the Science Board for your input and expertise.

Ten years ago, my poultry science professor introduced me to the idea that we could grow meat from animal cell cultures. As we have moved over generations from extensive to intensive agricultural production systems to create more food from less land, it seemed obvious to me that moving towards highly controlled systems to farm cells, instead of animals, would be the next paradigm for food technology. And because this particular type of intensification removes the need for whole, complex organisms, I suspect that producing meat from animal cell culture, rather than whole animals, should result in fewer viral epidemics, fewer climate-related catastrophes, and fewer externalized costs to the environment, public health,

and animal welfare. While these potential benefits do not pertain to food safety at the level of the individual consumer, they do pertain to food safety at a public health level. With our current production systems, you do not have to consume meat or dairy to be threatened by an antibiotic-resistant infection, an avian flu, or a foodborne illness.

Potential benefits aside, there are clearly many unknowns about producing meat from animal cell culture technology, and it is of utmost importance that the hazards, nutritional considerations, and production methods for this technology are well-understood to identify risks and ensure consumer safety.

I have dedicated my career to this work because I believe this transformative technology was inevitable. However, I want to ensure that it enters society in the most responsible way possible. So it is truly a pleasure to be here today.

Before I proceed with answering the six questions posed by the agency in today’s agenda, I would like to emphasize that there are multiple methods and multiple combinations of methods to produce foods

from animal cell culture technology. So that there is likely no “one size fits all” approach to production hazard, risk, or safety. It strikes me that existing FDA guidances for existing food and drug manufacturing should provide adequate initial frameworks for assessing the safety of many methods that could be employed to create food products from animal cell culture technology.

Question 1 regarding adventitious agents. Yes, adventitious agents could be plausibly introduced into culture from seed cells or culture materials. These adventitious agents could be of microbial, viral, or fungal nature, introduced by the collection of the original tissue, raw materials involved in the cell culture process, or human handling. However, there are already established tools that can be pulled from existing industrial bioprocesses that would be effective in identifying and managing these risks for animal cell culture technology.

There is appropriate existing guidance on creating, characterizing, and qualifying cell banks to ensure seed cells are appropriately identified and free

of contamination. And I believe that these could serve as the basis for cell-banking methods appropriate to animal cell culture technologies.

Question 2 regarding the cell culture process, previous cell culture experience tells us that the potential for contamination cannot be completely eliminated. However, the risk of contamination can be effectively minimized so as not to threaten human health. Establish protocols for existing industrial bioprocesses for food and drug manufacturing, such as aseptic technique, sterilization, and routine screening have successfully minimized contamination risk for existing food and drug products. These existing protocols could reasonably be applied to large-scale production of foods from animal cell culture technology with very low likelihood of risk to human health.

Question 3 regarding culture media, cell culture media are still being developed for all mammalian cell cultures, regardless of intended use. In general, we believe that it is very likely that the substances used in cell culture media would not be dissimilar to those used for other human applications,

including food. Again, we believe that existing guidances for cell culture and enzyme sourcing can serve as the basis of established operating procedures for animal cell cultures for food production to ensure safety. Similarly, the current advice from the agency on sourcing materials to be used in cell culture media can serve as the basis for developing practices for food production cultures.

Question 4 regarding scaffolding materials, most scaffolding materials would likely be composed of food-grade materials, such as cellulose, collagen, or chitin. These materials could be absorbed by the growing cellular matter or it could be intentionally removed from the final product and could easily be evaluated using existing food ingredient evaluation procedures to ensure safety. We note that novel scaffolding materials could create metabolites or residues in the cell culture process that remain in the finished food product. Such novel scaffolding materials, which could change in the culture process, may require safe evaluation but does not fall under existing food ingredient evaluation procedures and will

likely require food additive approvals prior to use.

Question 5 regarding errors in the culture process, for large-scale culture of a single cell type, there are existing protocols and assays for detection of errors in the culture process. The likelihood that harmful substances, such as metabolites or allergen, would be created are quite low. However, in the absence of peer-reviewed research on large-scale culture of all meat- and seafood-relevant cell types and species, it is hard to conclude definitively.

Further, there is a gap in FDA guidance around co-cultures or the simultaneous culture of multiple cell types and/or cell species. In this scenario, it would be important to understand how multiple cell types may interact in culture conditions. I do not believe there are existing frameworks for evaluating the safety of co-cultures across food or drug manufacturing, but New Harvest welcomes the opportunity to work with the agency and other experts in developing the background science to identify potential risks and hazards.

Question 6 regarding nutritional

considerations, nutritional considerations have always been a thorny area for evaluation. Because the fine composition of food from animals or plants differs based on genetics, husbandry, and food sources, preferring these analyses are often dependent on selecting the appropriate comparator.

We note that the animal cloning risk assessment provides an excellent methodology for determining the nutritional sufficiency of meat and milk. We encourage the agency to look to that paradigm for safety and nutritional evaluation.

It is very possible that meat produced through cell culture technology could exhibit a wide range of nutritional value, largely determined by the composition of the cell culture media during proliferation and differentiation of the cells in culture. I believe it would likely be that the nutritional profile of a meat produced from cell culture technology could be designed to be similar to conventional meat, either through manipulation of the cell culture media or through enrichment and fortification processes taking place post-harvest. I

would be curious to see if the bioavailability of certain nutrients would differ if they were incorporated into the product by the cell culture process compared to via post-harvest enrichment. For example, will iron be present in the heme or non-heme form in a final food product?

In summary, I believe that there are already frameworks in place from food and drug manufacturing that could assess and manage the risks of a cell-based meat manufacturing process. However, these existing frameworks come from both food and drug manufacturing. And there may be differences in the intended use in the route of exposure of the products evaluated by these existing frameworks and the intended use and route of exposure of a cell-based meat.

Further, while the frameworks may cover several processes for cell-based meat production, I am not sure that they can cover all future processes given that there are so many opportunities for novel innovation in the development of cell-based meat production processes.

The aforementioned co-culturing of multiple

different cell types is an example of an innovation where I have not seen prior guidance or frameworks for evaluating safety.

I have one additional point of note. The basis of good governance and good regulation is informed by evidence and peer-reviewed research. Federally funded research is an important part of this equation, perhaps because of the novelty of this research or perhaps because it pulls from expertise historically created in medicine but, instead, applied for food production. This research has not received meaningful federal support. The majority of research in the production of cell-based meats has come from venture capital-funded companies or from philanthropy-funded research organizations, like New Harvest. These funding streams have definitely brought the field to this point. However, for this technology to be fully realized, not just as a product but as a new paradigm for food production, we will need to see more support for academic peer-reviewed research.

Perhaps the identification and support of research initiatives that would both equip regulators

and minimize burden on innovators could be a good important way for the FDA, USDA, and perhaps the NIH and NSF, et cetera, and the burgeoning cell-based meat industry to work together. My organization, New Harvest, as a primary funder of academic research in this space to date would be a keen collaborator and resource in moving this forward.

Thank you to the FDA and the Science Board for your efforts to create a safe path forward for this technology.

DR. McLELLAN: Thank you very much.

We will now hear from the Good Food Institute, David Welch. David?

MR. RAGHUWANSHI: Before you begin, I do have your slides in .PDF. I called for some technical assistance to get that to be able to be broadcast. So if you don't mind, can we move on to the person that was scheduled after you and come back to you in just a minute?

DR. WELCH: Of course. Yep.

MR. RAGHUWANSHI: Is that okay? Okay.

DR. McLELLAN: Okay. That would mean we

would move on to Memphis Meats and Eric Schulze. Again, Eric, we will run a 10-minute timer with a 2-minute --

DR. SCHULZE: Yes. And do you have my slides?

MR. RAGHUWANSHI: Let me see. I don't think I received any slides from Memphis Meats. Same issue. It is .PDF. Give us a second. I think -- the one after you, Mike Selden from Finless Foods, I know they didn't send any slides.

MR. SELDEN: No slides.

[Laughter.]

MR. RAGHUWANSHI: Okay. Let's go to that one. And in the meantime --

MR. SELDEN: One of us is going to go.

MR. RAGHUWANSHI: Yes, eventually.

DR. McLELLAN: Thank you, Mike.

MR. SELDEN: Good afternoon. Thank you so much for allowing me to be here, now second, I guess. My name is Mike Selden, co-founder and CEO of Finless Foods, which I believe qualifies as a financial interest in this topic, but I do want to add that if I

wanted to get rich, I would have studied finance, not biochemistry. We started this company dreaming of creating a safer and more sustainable food supply.

In the next few minutes, I aim to lay out what Finless does, the safety emphasis that should be considered when creating a safe framework for cell-based fish, as well as some thoughts on what to call what we do as it relates to safety. I am aiming to address some concerns raised earlier today as well as inject some thoughts into the conversation that haven't yet been brought up. I have been frantically typing as you have been speaking.

Finless Foods is a company developing sustainable seafood using animal cell culture technology, which we call cell-based fish. We take a small sample of cells from a real fish and grow them out in order to create healthy and sustainable seafood without the presence of substances such as mercury or plastic. We are essentially working to create an environment that imitates the process of growing muscle inside of a fish outside of a fish. This means that everything, right down to the materials we use, are

attempting to closely represent the inside of a fish so that these cells do what they are naturally inclined to do, which is to divide and grow. A core aspect of our philosophy is that a fish in the context of food is merely a means by which humanity currently produces seafood and that we believe that animals might not be the ideal means to produce this seafood. We aspire to create a food system that can provide healthy fish meat efficiently on land, rendering the long transportation time from the water to people's plates obsolete. We hope that through this process, we can reduce food waste, spoilage, and deliver a fresher, safer, and longer-lasting food supply.

While the process for producing meat using animal cell culture technology at scale is not entirely determined as of right now, there is a large body of literature detailing safety protocols and tissue culture that we can draw from to guide us as this is quite far from a new process.

In the context of food, there are potential safety differences to consider when compared to traditional methods of meat production, most of which

have been laid out today. Many of the potential risk avenues present in conventionally produced seafood come from the fact that fish meat is harvested from animals, which have higher levels of bacteria than our near-sterile cell cultures do.

Although, as stated already, we can't know for sure, we do believe that there are inherently less risks in producing seafood outside of the body of an animal. One of the main potential differences I would like to bring up as it pertains to seafood, in particular, is that we have no reason to believe that any of our products will contain the mercury and plastic levels present in wild-caught fish or even the lower levels present in farm-raised fish. Large doses of mercury have the potential to impair the development and functioning of the brain and nervous system. Based on current evidence, carnivorous fish, at the top of the food chain, have the highest mercury levels because mercury is bio-accumulated, which means it can rise up the food chain and become concentrated at the top. Because of this, the FDA and EPA have advised that many large fish species be consumed in limited quantities by

at-risk groups, such as women of childbearing age. With our technology, we have the ability to bring these mercury levels down and have the potential to remove mercury as a concern entirely since mercury travels through a pathway that doesn't play a part in our means of production.

The effects of plastic found in wild-caught fish on the human physiology is less well-studied, but we believe it is still a cause for concern. Studies that have been done on how plastic consumed by fish can affect their physiology have been conducted, with some pointing to signs of liver toxicity and pathology, reduced feeding and shoaling behavior, and altered metabolisms.

Our process has no ties to the ocean other than the tiny starter culture. And so the recent studies indicating that there will be more plastic than fish by weight in the ocean by 2050 aren't of concern to people's health through the fish they eat if they are eating fish produced using animal cell culture technology on land.

Current wild-caught fish productions tied to

nature make for a less than stable food supply chain. Time and time again, it has been shown that a sizeable chunk of the fish that we eat in America is mislabeled. This is often because of supply chain instability. Using the processes we are developing, we hope to have a much higher level of certainty of how much fish can be produced, providing increased stability and making the mislabeling of fish a thing of the past or at least mostly a thing of the past.

Earlier, it was brought up that much of the science at lab-scale involves the use of single-use plastic and that this industry might cause more environmental problems than it solves. A study published in Nature this year concluded that fishing nets account for 46 percent of the trash in the Pacific garbage patch, with the majority of the rest composed of other fishing-industry gear, including ropes, oyster spacers, eel traps, crates, and baskets. We believe moving away from one-off experiments and towards mass production models will see our use of disposable materials decrease, but fishing will, unfortunately, remain the same.

At Finless, we focus on producing bluefin tuna specifically, an animal that is on and off the threatened species list. So in terms of waste, we assume that at first, our process won't be perfect due to unknown unknowns, but we are in any case moving the burden of human consumption of this keystone species away from the ocean ecosystem and onto land, where we can work to find more sustainable production solutions in a controlled environment.

One issue that was brought up today was the question of using serum, an example of which is FBS, fetal bovine serum, fetal calf serum -- it got called a lot of stuff today -- in the production process. I want to reaffirm that Finless will not be bringing products to the market that use serum in their production, only in the initial R&D process, where we will be setting up our initial cell lines. This means there is a point where R&D ends for each cell line. Our use of serum ends entirely for that cell line. And potential risks, such as prions, as they were brought up, can be tested for using methods explained in existing literature. After that point, we will not be

introducing serum to our process. Past this point, any potential vector for contamination due to agents, such as prions, that can be present in serum will be eliminated.

Serum usage in production goes against the mission of our company because using serum is both not sustainable and involving animal cruelty. It is also difficult to work with due to its high price, fluctuations in quality from batch to batch, and inherent properties that cause stir tank bioreactors to foam. On top of all of that, the supply is quite limited or wouldn't be able to create any sort of mass market product that uses serum as an input because there just isn’t that much serum produced on Earth in our current supply chain.

Another issue brought up today was long-chain fatty acids, like Omega 3 and Omega 6, and their levels present in fish. These fats are not produced naturally within the body or cells of any fish and in a lab setting are taken in via a consumption of plants and then travel up the food chain due to bio-accumulation. Because of this, they are currently added to fish feed

for farmed fish in order to imitate the nutritional content of their wild-caught equivalent. Our process is similar in that we, too, will need to add these fats to the feed we give to our cells.

Lastly, something that we feel very strongly about is that we must, in some way or form, potentially with qualifiers, use the correct terminology and label these cell-based fish as fish. When we produce cell-based tuna, we must ensure to use the word “tuna” somewhere in the name. And when we produce cell-based salmon, we must use the word “salmon,” et cetera.

The issue with potential allergens was brought up earlier. I would like to add on top of that that an estimated seven million, million, Americans are allergic to seafood. That is about 2.3 percent of the population. If one is allergic to animal-based seafood, that person has a high probability, I would say almost a 100 percent certainty, of being allergic to the seafood produced using our technology. And so labeling it in any other way has a large potential of creating a public health hazard for these millions of people.

An allergic reaction to certain proteins in current animal-based seafood can cause life-threatening anaphylaxis, a sudden, severe, potentially fatal reaction that results in low blood pressure and throat swelling, making breathing difficult. Seafood allergies can also cause a severe skin reaction or can trigger an asthma attack. For these reasons, we want to ensure that when people are choosing to buy food, they understand that what we make can produce these reactions in those that have allergies to seafood. Our technology is meant to create a safer option for our food supply. Proper labeling is essential in accomplishing this goal.

In conclusion, we believe that there are many variations in manufacturing methods specific to fish produced using animal cell culture that are relevant for food safety protocols. This does lend itself to a difference in potential hazards, many of which I have outlined in the past few minutes.

I am happy to provide additional information. And we will be citing sources when we submit written comment. I hope this session proves itself informative

and look forward to continuing the conversation with all of you in forums, both open and beyond. Thank you very much.

DR. McLELLAN: Thank you.

We will move on or back, rather, to the Good Food Institute and David Welch. David?

DR. WELCH: Yes? Good afternoon.

DR. McLELLAN: If you would just indicate, say, “Next slide,” we will advance for you.

DR. WELCH: Got it. Okay.

DR. McLELLAN: Thank you.

DR. WELCH: Good afternoon. And thank you for the opportunity to provide comments. And thank you for the work that you are doing to better understand cell-based meat. I am David Welch. I am the director of science and technology at the Good Food Institute. And I have no financial conflicts of interest.

Next slide, please. We have heard many times today, starting with Dr. Gottlieb and through others throughout the day, that the core technology surrounding the production of cell-based meat at scale is well-understood. I would also like to reference the

background materials that were provided for today's meeting and the presentation by Dr. Mozdziak at FDA's July 12th public meeting at well, which provides a great deal of background on this process.

I would like to summarize it with this schematic quickly. Starting on the left, a small biopsy of cells is taken from an animal. These cells are then proliferated or expanded in a bioreactor with cell culture media. Once there is a sufficient number of these cells, these undifferentiated cells, a change in cell culture conditions pushes the cells to differentiate into meat, which is primarily comprised of muscle, fat, and connective tissue.

Next slide, please. One can segment the technology of cell-based meat production into four areas. There are the cell lines, cell culture media, scaffolds, and bioreactors. I would like to step through each of these briefly and then talk about some of the guidelines and potential risks associated with each of these areas.

Next slide, please. Cell lines, there are many factors can access the cells to produce cell-based

meat from a variety of different tissue types. And the cells that they use will depend on the specific application and the established process. They could be pluripotent in nature, so induced pluripotent stem cells that were discussed earlier. They could be multipotent or specialized, such as myosatellite cells. But, irrespective of the type of cells, these cells need to exhibit proliferative capacity. They need to be able to multiply continuously, and they need to exhibit stability through each of those multiplication phases.

Next slide, please. For these cells to grow and differentiate, they require nutrients in the form of cell culture media, the basic nutrients that these cells need to grow, primarily salts; sugars; and amino acids; and, as discussed several times today, growth factors that can control the behavior of the cells, keeping them in an undifferentiated state or pushing them towards muscle fat or connective tissue.

Next slide, please. If we are talking about more complex cell-based media structures, it is likely that scaffolds would be required to provide structure

to those cells and those tissues. We believe or we expect that these scaffolds would be created from materials that are either biodegradable or edible in nature.

Next slide, please. For cell-based meat to function at large scale, it is likely that these processes will take place in large bioreactors. There are two main types of bioreactors that are used in other applications, such as biomedical processes or food applications, that can be adapted for use in the manufacturing of cell-based meat. The first is a stir tank bioreactor. This is a very common bioreactor that is used both in food applications and in the biomedical industry. And the second is tissue profusion bioreactors that are today primarily used in biomedical applications, such as cell therapy, and will likely require additional engineering for scale-up before they can be used at large-scale and cell-based meat applications.

Next slide, please. I would like now to talk about some of the potential risks that were outlined in the questions provided for today's session. Regarding

animal cell lines, we expect these cell lines to be similar to those used in existing applications with FDA oversight. And, as a result, there are existing FDA guidance documents that provide guidelines and well-established tests for the detection of adventitious agents. I have listed a couple of examples of them there, and I will call out the CMC for vaccine and related products that was provided as one of the background reading materials.

Next slide, please. Regarding the production of substances during the culture process, we expect the cell culture media to contain ingredients that are widely used in the food industry and that, as a result, their safety, the safety of those ingredients, is well-understood and documented. In addition, the medium may also contain recombinant proteins or small molecules present at low concentrations. And, again, we expect these to be produced through methods that are currently used to make enzymes and other food-processing aids routinely used in the food industry.

There are numerous GRAS submissions -- I have listed some of them here -- and also an FDA guidance

document on enzyme preparations that provide both well-established and relevant methods and also tests for the assessment of these ingredients as part of the cell culture media formulation.

Next slide, please. Regarding scaffolds, the scenario, we expect the scenario to be very similar to that of cell culture media in terms of production of substances during the cultural process. These scaffolds, as I mentioned earlier and that was discussed several times today, are likely to be comprised of edible materials. An alginate and cellulose are two very good examples of materials that are already used to create scaffolds in cell therapy applications.

And, as with cell culture media, there are guidance documents, the same ones I referenced on the previous slide, and GRAS submissions that provide strong, established relevant methods and tests for the assessment of risks associated with scaffolds during the culture process.

Next slide, please. Regarding the potential harmful substances that are produced during the culture

process, it is likely that non-optimal cell culture processes or conditions in the bioreactor could cause cells to create substances at levels different from those in an intact animal. I have listed some examples of those here. One is that growth factors or other molecules could be produced by intra- or intercellular signaling. They could be the production of unintended or abnormal levels of metabolites. Genetic and epigenetic drift could cause layered protein expression levels. And endogenous retroviruses that were discussed earlier today or other species' specific viruses could be produced.

As with the case in the previous slides that I mentioned, there are already well-established and -documented controls and assays. Those could require the PCR technology or chromatin in immunoprecipitation to detect abnormal levels of such substances.

Next slide, please. Regarding nutrition, we expect the cells produced through the process of cell-based meat manufacturing to physiologically mimic the cells within animal muscle tissue and conventional animal meat. The animal cloning risk assessment; the

numerous GRAS submissions, some of which I have mentioned here; and other guidance documents involving meat-and poultry-based ingredients that are used in meat and poultry products, again provide guidelines and establish tests to compare the nutritional and compositional qualities of cell-based meat to that of conventional meat.

Next slide, please. In summary, we expect cell culture technology to enable the production of high-quality protein foods without posing risks that cannot be managed effectively through the use of well-understood and -established controls by responsible manufacturers.

As we have heard many times today, the core technology, the core science for cell-based meat production is very well-understood. There could be cellular events that are unique to the manufacturing of cell-based meat, but these can be characterized and assessed with existing well-established tests. In addition, documented guidelines and tests exist that can be applied to cell-based meat to identify and characterize potential hazards and assess risks. And

these risks are well-understood, as we heard from Dr. Sheets earlier. We understand these risks. And we understand the controls that we can put in place to monitor and assess these risks.

And, finally, the FDA can regulate this industry by using science and risk-based regulatory approaches under its existing authorities as well as its extensive experience to help ensure the safe production of cell-based meat.

And the final slide is just to thank you again for the opportunity to provide comments.

DR. McLELLAN: Thank you.

Our last presentation will be Eric Schulze from Memphis Meats.

DR. SCHULZE: Good afternoon. My name is Eric Schulze, and I am the vice president of product and regulation at Memphis Meats. Memphis Meats is a research-stage cell-based meat company based in Berkeley, California. We hope to commercial our cell-based meat products here in the United States in the near future. I look forward to continuing to work with the FDA and USDA and other stakeholders in implementing

a clear, predictable, and risk-based regulatory framework for these products. Indeed, as Commissioner Gottlieb himself said, we "need a regulatory process that is clear, has bright lines, and does not stall this opportunity and gets this right."

Cell-based meat products are familiar meat, poultry, and seafood products produced ex vivo, meaning cells that would normally grow to fermentable tissues in an animal are, instead, grown, matured, and harvested in a controlled production environment outside of the animal. Our staff in less than 3 years has grown to 34 people. Our scientific team is comprised of molecular biologists, geneticists, analytical chemists, applied mathematicians, tissue and mechanical engineers, and muscle and stem cell biologists, each possessing advanced degrees in their respective fields and over 30 years of large-scale bioprocess experience. We understand that sound regulatory policy based upon scientific evidence and established principles should guide the safety evaluation of any product under consideration, novel or not. And based upon our experience and research, we

believe that current scientific evidence and understanding as well as key regulatory process demonstrates the risks associated with cell-based meat products are well-understood and can be effectively managed using existing regulatory paradigms and well-established controls.

We appreciate the opportunity to address the key safety and nutritional considerations relating to cell-based meat production in response to the questions raised by FDA and discussed earlier today.

Next slide, please. Currently, cell-based meat production is a three-stage system. First is cell and tissue procurement and qualification. Second is tissue production. And third is tissue qualification and food production. The final stage generally involves food processing and packaging activities that are comparable to those used for conventional meat, poultry, and seafood. Walking through the process briefly, the first step primarily involves identifying, characterizing, and qualifying target cell populations for cell banking and production. The second stage primarily involves cell growth, maturation, and

production at scale following the harvest of mature tissues, which might include adipose, connective, integumentary, in addition to myogenic tissues if the tissues are qualified for release or storage. The final stage involves entrance of our tissues into a conventional meat food-processing environment where the tissues are, like their conventionally produced counterparts, processed into meat food products.

Next slide, please. As with any food production or biological manufacturing process, there are potential hazards as well as effective mitigation methods. Cell-based meat production is no different. And, as Dr. Sheets emphasized many times today, a lot is known about the risks and what controls can be used to manage those risks.

On this slide, we list potential foreseeable hazards and established controls organized by production element. In general, there are four overarching production element categories for cell-based meat production. These include cell stocks and cell substrates; second, raw materials, such as cell culture media components and other non-cell substrate

materials; process equipment, such as the cultivator systems; and, finally, personnel in the production facility itself.

With respect to cell stocks, a primary concern is the potential for introduction of adventitious agents into the manufacturing process. Rigorous screening, characterization, and qualification of the master cell bank are methods that mitigate such hazard and have been used widely to effectively manage risk in therapeutic settings. Raw material inputs contamination of pathogenic organisms or chemical toxicants are foreseeable hazards, which can be adequately controlled by sourcing from qualified vendors with suitable control systems implementing a release specification plan and proper prevention processing controls, such as filtration or heat treatment procedures.

There are similar hazards for processing equipment, which can be adequately controlled through proper equipment design and execution of robust sterilization procedures and maintenance. Implementation of proper sanitation procedures and

precaution, coupled with proper facility and utility design and maintenance can also mitigate against contamination from personnel and the production facility itself.

Next slide, please. These hazards are well-understood. And there are well-established methods for controlling that help assure the production of safe food. Indeed, as Dr. Paul Mozdziak noted in his presentation during the FDA public meeting on July 12th, animal cell culture “technology has been around for a very long time and is ‘well-established.’” And in terms of the process, we understand the potential failure points, and we know how to monitor and control the process. As Dr. Mozdziak also explained, these methods include aseptic controls and monitoring methods, proper characterization of the master cell bank, and quality control points typically associated with cell bank production.

Next slide, please. While it is possible that adventitious agents such as bacteria, fungi, and viruses could be introduced into culture materials, these risks are well-known and understood. Potential

sources of adventitious agents generally fall within three categories, including cell stocks, non-cell raw materials, and the human staff. There are well-established tools that could be applied appropriately to control for risks encountered in cell-based meat production, which I will briefly outline.

Next slide, please. Existing FDA guidances, one of which is provided in the FDA background materials for this meeting and is cited extensively in our presentation, provide well-established principles, testing methods, and other controls that could be applied appropriately for managing risks related to the potential introduction of adventitious agents. We identify and further describe established controls for cell banks and raw materials on the slide. In general, these controls include appropriately characterizing and qualifying the master cell bank prior to production and deploying a rigorous raw material qualification and monitoring program and as explained by Datar, M. Betti in the article cited in FDA's background materials, the basic industrial cell culture manufacturing conditions are "controlled and manipulatable" and cell-based meat

products, again “offer a level of control unattainable by traditional livestock methods of producing meat,” Specifically in “preventing the uncontrollable, unpredictable complications present in livestock production.” Beyond this work, we note that all of the technical literature cited in FDA’s background materials contain cross-referenced and highly validated methodologies and known contamination points consistent with our overview.

Next slide, please. These are several lessons that can be drawn from prior cell culture experience in evaluating cell-based meat production. No cell culture is entirely impervious to contamination, but these risks are well-known and can be effectively managed. Modern industrial bioprocesses operate successfully at large scales based on effective use of preventative controls and detection methods that minimize or eliminate exposure pathways to hazards. This includes the prevention, detection, and control of adventitious agents into the manufacturing process from cell stocks and raw material inputs. In addition, exposure pathways can be minimized or eliminated, such

as by appropriate quality control program.

Next slide, please. Leaning to substitutes using the cell culture, cell culture media, also known as cell feed, is a liquid matrix containing all essential components for metazoan cell viability, including amino acids, sugars, trace elements, vitamins, lipids, fatty acids, and proteins, and growth factors. We currently use materials that are widely used in the food supply and are generally recognized as safe or otherwise approved under FDA regulations. We expect that other producers are doing the same. Nonetheless, substitutes used in cell culture media and structural materials can be evaluated using traditional food ingredient evaluation procedures under FDA's GRAS, food additive, and color additive frameworks consistent with FDA guidances and key precedents listed on this slide.

Next slide, please. As has been discussed over the course of today and in FDA's background materials, the risk of potential production of harmful substances is well-understood and can be effectively managed. There are well-established assays to detect

the presence of such substances as process and verification controls to prevent the distribution of contaminated product. The risk of harm from latent viruses is highly unlikely based on current practice and research and can be effectively managed. Other potential errors are able to be detected and prevented through routine quality control testing.

Next slide, please. Regarding nutritional properties, we expect cell-based meat products to be substantially the same as conventional products by design. Meat is a complex tissue with a known range of variation in nutritional characteristics. Nutrient variation in conventionally produced meat can be a result of animal genetics and age, environmental factors, and tissue source. Nonetheless, well-established test methods exist to compare nutritional and compositional qualities of cell-based meat to conventional counterparts, including those cited on this slide. And in early analysis, our testing reveals a high degree of similarity in key nutritional parameters, including macro nutrients, amino acids, fatty acids, and lipids.

We agree with the position put forth by Datar, M. Betti that a key component of cell-based meat development is ensuring that the product has the full complement of nutrients available, particularly in comparison to conventional meat. We believe this not only to be achievable but that cell-based meats could be designed to have even more enhanced nutritional profiles than products currently on the market.

Next slide, please. In conclusion, the risks associated with cell-based meat food products are well-understood and can be effectively managed through risk-based prevention, monitoring, and control measures. These control measures can be applied through a well-executed food safety program. Risks due to adventitious agent introduction can be mitigated through the characterization and qualification of the master cell bank and raw materials. Existing FDA guidances and industry best practices for large-scale cell culture manufacturing, including those provided in the agency’s background materials, can be appropriately applied to the production of cell-based meat. The regulatory status of components in cell culture meat

and structural supplements should be assessed. And where unclear, existing GRAS, food and color additive frameworks, as applicable, should be used for the evaluation.

The risk of harm from products or metabolites arising from process variations is well-understood. And it can be controlled effectively through these of testing and product release specifications. And we expect the nutritional characteristics of cell-based meat products to be substantially the same as that of conventional meat comparators by design.

On behalf of Memphis Meats, we thank the Science Board for your time and consideration and the FDA and USDA for convening the important meetings that are taking place this week. Thank you.

DR. McLELLAN: Thank you.

Are there comments from the board members, having heard the open testimony?

[No response.]

FINAL THOUGHTS AND CLOSING COMMENTS

DR. McLELLAN: Let me close with a brief comment. I will say this, that I believe personally

that any effort to find new foods, new food sources is critically important. Though all of us will go to bed tonight with a full tummy, there are hundreds of millions that will not tonight, will not. And if you think that is challenging at seven billion, add another billion to that or another two billion faces to that. Finding food sources is critical. And it is a challenge for society that we have got to search everywhere for. This may be an opportunity, and it is worth exploring.

Equally, FDA, it is critical you understand our role is not to advocate for a process or a food but to advocate for science being used in all of your decision-making, hence our questions and queries that might at times feel a bit uncomfortable.

Thank you all for your time and listening. It has been great and enjoyable. And I wish you all safe travels. Thank you.

[Whereupon, at 4:23 p.m., the meeting was adjourned.]