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FDA PUBLIC WORKSHOP

DEVELOPING ANTIFUNGAL DRUGS FOR THE TREATMENT OF
COCCIDIOIDOMYCOSIS (VALLEY FEVER) INFECTION

DATE: Wednesday, August 5, 2020

TIME: 5:30 p.m.

LOCATION: Virtual Silver Springs, MD 20903

REPORTED BY: Janel Folsom, Notary Public

APPEARANCES:

JOHN FARLEY

DAVID STEVENS

ERIN ZEITUNI

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ANTONINO CATANZARO

Job No. CS3856656

<p style="text-align: right;">Page 2</p> <p>1 ROYCE JOHNSON 2 JOHN REX 3 ED GARVEY 4 DAVID ANGULO 5 GARETH LEWIS 6 DAVID LARWOOD 7 NEIL AMPEL 8 SUMATI NAMBIAR 9 10 11 12 13 14 15 16 17 18 19 20 21 22</p>	<p style="text-align: right;">Page 4</p> <p>1 we ask all of our speakers and discussants to speak as 2 clearly as you can, and also stick to the time so that 3 we can stay on agenda. 4 For the speakers and panelists, you 5 will a phone icon in the upper bar on the left. It's 6 green. You'll see that before your session or panel 7 discussion, and at that point you can click on the 8 phone icon and have the meeting call you and you'll be 9 able to speak and be heard. 10 Note that -- and particularly for the 11 audience -- when people are unmuting their phone to 12 speak, there's a bit of a delay in the system so it 13 takes a few seconds longer than you expect. 14 If you're not a speaker or panelist for 15 this particular session, you'll be in listening mode 16 like the audience, using your computer speaker and you 17 can control that using the speaker icon. 18 If anyone happens to get cut off due to 19 an internet issue, just close Adobe and then use the 20 link to go ahead and rejoin the meeting and that 21 should go well. 22 I note that speaker slides, transcripts</p>
<p style="text-align: right;">Page 3</p> <p>1 P R O C E E D I N G S 2 JOHN FARLEY: -- from the Office of 3 Infectious Diseases at the FDA. I just want to do a 4 quick sound check and make sure that my audio is okay. 5 Judy, could you confirm audio? 6 JUDY: It's fine, John. We can hear 7 you. Thank you. 8 JOHN FARLEY: Excellent, excellent. 9 Good morning, everyone, and welcome to our workshop 10 this morning. This is our -- I want to thank 11 everyone, particularly the speakers and panelists 12 who've worked hard to prepare presentations to 13 facilitate an excellent discussion today. 14 This is our second virtual workshop. 15 We had our first one yesterday. It was in the middle 16 of a tropical storm hitting Washington and actually 17 went rather well. There's been lots of preparation to 18 see that this workshop goes smoothly. 19 We're using a platform that some of you 20 may not be familiar with, so I just want to open with 21 just a few tips for the day and things that I learned 22 the hard way yesterday. So, first of all, of course,</p>	<p style="text-align: right;">Page 5</p> <p>1 and recordings will be available on the meeting 2 webpage in the next few days. 3 So, the purpose of our workshop today 4 is to hold scientific discussions to better understand 5 the current state of coccidioidomycosis and focus on 6 potential strategies to facilitate the development of 7 drugs that can safely and effectively be used to treat 8 cocci. 9 Now, cocci presents both challenges and 10 opportunities due to the spectrum of disease and the 11 need for products to address patient needs throughout 12 this spectrum. For antifungal drugs we all recognize 13 that there are both scientific and financial 14 challenges, but we will make progress when we work 15 together -- government scientists, academic 16 researchers, healthcare providers, patients and drug 17 developers. Let's frankly discuss those challenges 18 and get ideas on the table for moving forward. 19 So, I'm looking forward to a really 20 good discussion today. And it's my pleasure to 21 introduce our co-chairs for Session 1, Susan Hoover 22 from Stanford Health, and Lanling Zou from NIH. I'll</p>

<p style="text-align: right;">Page 6</p> <p>1 turn the microphone over to them at this point for our 2 first session. Thanks very much and welcome. 3 SUSAN HOOVER: Good morning. I'm Susan 4 Hoover, as John said, at Stanford Health. And my co- 5 moderator Lanling Zou is in the Bacterial and Mycology 6 Branch of DMID at NIH. This first slide depicts all 7 the speakers -- ourselves, the moderators, and all the 8 speakers of Session 1. 9 Our first speaker is David Stevens. 10 Dr. Stevens is Professor of Medicine at Stanford 11 University Medical School and President of the 12 California Institute for Medical Research, San Jose, 13 and PI of its Infectious Disease Research Laboratory. 14 DR. DAVID STEVENS: Okay, these are the 15 topics I was asked to cover. I hope everybody can 16 hear me. I assume they can, and we'll get started. 17 This microbe has a very interesting 18 life cycle, which I don't have time to get into, but 19 there are two points on this slide that you need to be 20 aware of: One is that there's a completely different 21 morphological form cycling in the body -- that's the 22 right half of this slide. And the left half is what</p>	<p style="text-align: right;">Page 8</p> <p>1 this microbe can be found, but it's the predominant 2 one. 3 And this gets into the epidemiology of 4 this organism. The prisons in California -- state 5 prisons have been built in a chain along the central 6 valley. There's a number of reasons for that and one 7 is the cost of land. But as a consequence of putting 8 prisons in these places where cocci is found in the 9 soil, there have been outbreaks amongst prisoners and 10 guards to the point where a federal judge has actually 11 made a ruling about who can be put into these prisons, 12 depending on their risk factors. 13 So, as far as we understand it now, 14 there are two species, immitis and posadasii, and as 15 far as we know, the clinical disease caused by the two 16 different species is identical. 17 This slide talks about the 18 epidemiology. It's a fairly recent take. It takes 19 you up to 2018, and I think it's obvious that cocci is 20 on the rise. And there's a number of reasons for that 21 but two of them are -- one is increasing urbanization 22 in the endemic areas, and another relates to the</p>
<p style="text-align: right;">Page 7</p> <p>1 goes on in the soil. And the second thing you need to 2 know from this slide is that it's the soil that's 3 important for the epidemiology of this organism 4 because it is arthroconidia growing on hyphae in the 5 soil that releases the spores that infect you. 6 This slide shows the distribution of 7 the disease. It's a new world disease. And since 8 this slide was made, there have been some new areas 9 discovered in Brazil, Guatemala and Colombia, but 10 notably in the U.S., sites of endemicity have been 11 discovered in both Oregon and Washington. And with 12 global warming, the range of cocci in the soil is 13 expected to increase. 14 This is a more close up picture of the 15 area in the U.S. and Mexico. In the Lower Sonoran 16 Life Zone is what the blue describes here. This is a 17 dry region with hot summers and mild winters and 18 alkaline soil, sparse floras and typically at a low 19 altitude. 20 So, this is a typical picture of where 21 you might find coccidioid in the Lower Sonoran Life 22 Zone. This is not the exclusive life zone in which</p>	<p style="text-align: right;">Page 9</p> <p>1 annual rainfall cycles that occur. 2 So, we estimate that there are about 20 3 million people who are at risk of this infection. 4 This would include residents, people who spend their 5 winter escaping northern climates, other tourists, 6 other travelers, and the military bases that are in 7 the endemic areas. And the best guess we have about 8 the number of infections per year is 200,000 per year. 9 And this is a very underreported disease. And we 10 estimate that illness, frank illness occurs in about a 11 third of people who are exposed, which would amount to 12 about 67,000 infections, patent infections per year. 13 And we'll talk a little bit more about that 14 distribution. 15 So, this is how -- a principal way the 16 organism is spread in large numbers of people being 17 infected at the same time, and this is a dust storm, 18 which is fairly typical in some of the endemic 19 regions. Phoenix, for example, or Kern County in 20 California. And the dust storm, which kicks up clouds 21 of dust, also kicks up clouds of arthroconidia, and 22 they're about to descend on the homes of these people</p>

<p style="text-align: right;">Page 10</p> <p>1 who have moved into the endemic area and never had an 2 experience before with cocci. 3 Another way that the disease can spread 4 is through cataclysmic climate events. This picture 5 was taken during the earthquake in Northridge, 6 California, and you can see how much dust was kicked 7 up during this episode. And as a consequence there 8 were large numbers of cases in the area of the 9 earthquake -- cases of cocci, secondary to people 10 breathing in the dust that had been disturbed. 11 One of the things we might look forward 12 to in the future is a plan -- actually, construction 13 has started -- for a high-speed bullet train in 14 California to connect up the San Francisco and Los 15 Angeles areas going through the Central Valley. And 16 you can imagine the consequences for the workers who 17 will be working on this bullet train. 18 The picture at the left is not actually 19 workers on the bullet train; these are archaeology 20 students and they tend to dig in Indian middens, and 21 when they do, a lot of dust is thrown up into the air 22 and there have been many outbreaks of archaeology</p>	<p style="text-align: right;">Page 12</p> <p>1 that the consequences of coccidioidal infection not 2 only to man but also to his domestic animals. This is 3 a patient I consulted on. This is Belle, and Belle 4 has disseminated cocci. And this adds to the economic 5 consequences of this infection. And Lisa can talk 6 more about this. 7 So, in the humans who have the 8 symptomatic infections that we talked about, the 9 impact is like this: The average number of days that 10 patients feel ill is over 200, and the average number 11 of days that they miss work or school is longer than a 12 month. And this Congressperson has estimated that the 13 costs to California over a decade amount to about \$2 14 billion. 15 Another problem with the epidemiology 16 is that doctors in the endemic areas are undereducated 17 about cocci. And various studies have indicated a 18 range but slightly more than 50 percent of doctors 19 test community-acquired pneumonia in the endemic areas 20 for cocci. And in Arizona, about a third of the 21 community-acquired pneumonia is cocci. And about more 22 than half the patients with cocci have received</p>
<p style="text-align: right;">Page 11</p> <p>1 students following one of these digs where they were 2 perturbing the dust. 3 The right side is also not related to 4 the bullet train. That's a picture taken on 5 Interstate 5, which runs down the central valley. You 6 can see a dust storm approaching, and you can imagine 7 what the consequences would be for the people driving 8 on I5 at that time, especially if they have their 9 windows down. 10 Another way that the disease can spread 11 is by fomites traveling from non-endemic -- traveling 12 to non-endemic regions from endemic regions. This 13 shows three of the culprits that have been implicated 14 in that kind of spreading. And another source of 15 infection is laboratory accidents. A typical story 16 would be something occurring in a non-endemic region 17 where a clinical microbiology lab person would open a 18 plate because there's an interesting looking fungus on 19 the petri dish, and in the course of that, manage to 20 infect not only themselves but everybody else in the 21 laboratory. 22 And this picture I put in to remind me</p>	<p style="text-align: right;">Page 13</p> <p>1 antibacterials for their condition prior to diagnosis. 2 Antibacterials, obviously, wouldn't help. And they've 3 had three visits to the doctors before the diagnosis 4 is successfully made. 5 So, the picture, as we understand it -- 6 we talked about estimated 200,000 infections a year, 7 so multiple everything on the slide by about 200. But 8 about -- for every thousand infections, we estimate 9 that 600 of them are asymptomatic. These people would 10 experience a skin test conversion but not necessarily 11 any symptoms. And 400 of them will be symptomatic. 12 We'll talk about that in just a moment. 13 And from these cases, there will be 50 14 pulmonary residuals, which means that there will be 15 radiographic abnormalities that people will walk 16 around with for the rest of their life as a souvenir 17 of the coccidioidal experience. 18 And then, lastly, from the symptomatic 19 cases, there are five disseminated cases and it's 20 really these five cases, where the disease spreads 21 outside the chest, that occupy the major efforts and 22 attention of the medical professionals dealing with</p>

<p style="text-align: right;">Page 14</p> <p>1 these five per thousand who have disseminated disease. 2 This shows two of the pulmonary 3 residuals that are seen. On the left is a stable 4 cavity, and on the right a nodule. And if you 5 radiograph probably 100 people at random in 6 Bakersfield, you would find a number of them walking 7 around with these x-ray abnormalities, not at that 8 time causing them any clinical difficulties. 9 And the 40 percent of the patients who 10 have the respiratory illness can range from anything 11 that appears to be like flu up to community-acquired 12 pneumonia, and then there's a range within community- 13 acquired pneumonia. It can be a walking-type 14 pneumonia all the way to an acute respiratory distress 15 syndrome. There are some skin eruptions that 16 accompany this respiratory illness and the onset is 17 generally 1-3 weeks after they inhale arthroconidia. 18 And the big question at this time is 19 whether treatment would affect these primary 20 infections; either make the symptoms less or shorten 21 the duration, maybe even prevent dissemination. 22 That's an unknown -- an important unknown question at</p>	<p style="text-align: right;">Page 16</p> <p>1 disease, and what happens is there are successive 2 waves of cavities, modules, fibrosis and progressive 3 destruction and loss of function lung tissue as the 4 disease progresses. 5 The other bad way things can go is to 6 disseminate from the chest. And we recognize that 7 there are certain risk factors that predispose to 8 this. It more commonly happens in males than females, 9 it happens at a very high degree in people who are 10 immune compromised -- and we're going to talk about 11 that in some detail -- patients with congenital 12 immunodeficiencies are at risk of disseminating once 13 they have a primary infection. 14 The combination of pregnancy, 15 particularly in the second and third trimesters, seems 16 to be a bad combination with cocci with an increased 17 risk of dissemination and a bad course once it 18 disseminates. And there's a certain racial 19 predisposition to risk of dissemination. People of 20 Filipino ancestry are at the highest risk, then 21 African Americans, native Americans, Hispanics, other 22 Asians. All of those appear to be at greater risk</p>
<p style="text-align: right;">Page 15</p> <p>1 this time. 2 This is a radiograph of a primary 3 pulmonary infection due to cocci. There is nothing 4 specific about this in the differential diagnosis of 5 other causes of community-acquired pneumonia. And 6 this is two of the types of skin rashes that may occur 7 during the primary infection. What these patients 8 experience -- fatigue, fever, chills, etc., cough, 9 sputum production, all these symptoms, again, are not 10 specific for primary cocci infection but can be seen 11 in other kinds of community-acquired pneumonia, and 12 there's a differential diagnosis issue because of the 13 non-specificity of these signs and symptoms. 14 So, once -- if the infection doesn't 15 resolve with the durations I talked about earlier, 16 there's one of two bad ways that things can go: One 17 is the infection, instead of resolving in the lung, 18 can go on to produce a chronic pulmonary condition. 19 And the other, as mentioned, is to disseminate outside 20 the lung. 21 This is a picture of what can happen if 22 the patients develop a chronic pulmonary form of the</p>	<p style="text-align: right;">Page 17</p> <p>1 than do whites of disseminating the disease. 2 And what happens when it disseminates, 3 it's caused by hematogenous spread from the lung, and 4 a few months after the primary infection it will 5 either be manifest in the skin, it can go to bone or 6 joints or other sites. And the worst possibility is 7 the meningeal form of the disease. And, furthermore, 8 in all these sites there's a tendency to relapse 9 either after a successful resolution of a focal site, 10 it will come back, or even after successful therapy, 11 the natural history of this disease involves cycles of 12 relapse, recrudescence, and then, hopefully, remission 13 again once they are retreated. 14 This shows examples of the cutaneous 15 form of the disease. The patient on the right has 16 multiple granulomas of the skin, the patient on the 17 left has a soft tissue abscess with an ulcer draining 18 puss. And this unfortunate gentleman is showing you 19 in his bone scan that he has multiple sites of 20 skeletal involvement. You can see he's got multiple 21 sites in his skull, both shoulders, a couple of ribs, 22 there's some sites in his vertebrae, in the pelvis, in</p>

<p style="text-align: right;">Page 18</p> <p>1 his -- one of his ankles. And all of these are 2 destructive lesions due to cocci. 3 Another bad place that dissemination 4 can go to is the eye. And particularly if the retinal 5 involvement is near the macula, the patient can lose 6 vision, which may be permanent. And the lymphatic 7 system is another site of dissemination of disease. 8 (Oops, I've lost my...okay, sorry.) 9 As I mentioned, meningitis is the worst 10 complication. And there are, we estimate, about 200- 11 500 new cases of meningitis a year. This disease had 12 a natural history. Before the treatment was 13 available, we understood that the disease was fatal 14 within two years without treatment. So, a worst 15 prognosis than untreated lung cancer. And even with 16 the onset of treatment, there are many stroke events 17 that are associated with progression of the disease, 18 hydrocephalus can occur and compression of the spinal 19 cord. 20 Another manifestation of central 21 nervous system disease is a space-occupying lesion in 22 the brain and this is in the differential diagnosis of</p>	<p style="text-align: right;">Page 20</p> <p>1 2020? With a massive increase in transplantation as a 2 treatment modality for a number of conditions and a 3 massive use of immunosuppressives for a number of 4 conditions, this has become a huge problem in endemic 5 areas. And Janis could speak to this in more detail. 6 Another group that's at risk with 7 having a bad course of cocci are the HIV-infected 8 persons. And the disease in the HIV infected is about 9 20 times more common in endemic areas than non- 10 compromised persons. And a low CD4 risk factor 11 appears to be the major risk factor for the 12 development of progressive disease. And the cases 13 appear to be mixtures of new infections or 14 reactivation of old disease. 15 I'm not going to really talk about 16 treatment. I understood John was going to talk about 17 this some more but I think that's changed a little bit 18 with the latest iteration of the program. But I just 19 want to mention one approach to treatment because I 20 need to have it understood what I'm going to talk 21 about next, which is trying to come to evaluations of 22 the course using trial endpoints.</p>
<p style="text-align: right;">Page 19</p> <p>1 brain abscess. And this patient is showing a 2 cerebellar brain abscess due to cocci. 3 We appreciated early on that there was 4 a special course that occurred in immunocompromised 5 patients, and in this particular series, about half of 6 the patients had disseminated disease. And you'll 7 remember, I talked about in healthy persons, a 8 dissemination rate of 5 in 1,000. So, this is 100 9 times the rate in non-compromised persons. And the 10 risk of reactivation appeared to occur in persons who 11 were receiving immunosuppression for some medical 12 condition or experiencing a disease which in itself 13 was immunosuppressive, such as, for example, Hodgkin's 14 Disease. 15 And it also teaches you that viable 16 cocci organisms must be living in you after an initial 17 infection. Even if you've successfully resolved it on 18 your own or needed treatment and the treatment was 19 successful, the bug is with you -- and won't bother 20 you, but if something immunosuppressive happens to 21 you, you are at risk once again. 22 So, what's the consequence of that in</p>	<p style="text-align: right;">Page 21</p> <p>1 Our approach has been to treat 2 disseminated patients -- I'm not talking about 3 meningeal patients who require special treatment -- 4 but treat patients with oral azoles for a minimum of a 5 year or six months after the disease becomes inactive, 6 whichever of those two is longer. And use 7 amphotericin preparations if the lesions are in 8 critical locations or if the patient is worsening 9 rapidly because amphotericin is more rapidly acting 10 than azoles. And the surgeons have a role to play in 11 some of the manifestations of the disease, 12 particularly in bone and in soft tissue. 13 So, scoring systems have been developed 14 for therapeutic trials and have proven useful, and 15 there's experience that goes along with them. The 16 patients were initially scored according to their 17 culture-confirmed sites of disease, their serologic 18 titer, and the extent of lesions. And the sum of the 19 points pretreatment was their baseline score. A 20 successful response was considered a reduction of the 21 baseline score by 50 percent or more within a set 22 period of time.</p>

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<p>1 And because cocci tends to improve 2 relatively slowly, scoring was done at three-month 3 intervals. And far from ideal, the scoring system 4 does allow physicians to estimate a total body burden 5 of disease and follow that index in the course of 6 treatment. So, this is an example of a scoring system 7 that's been used. There are points assigned to 8 symptoms, to physical exam, to the height of the 9 serologic titer, to culture positivity.</p> <p>10 And the last point that I was asked to 11 address, to finish up, was -- is productive 12 collaboration in clinical trials with Latin American 13 centers possible? And my personal perspective on this 14 is a very resounding yes. I show here some of the 15 studies that it's been my privilege to collaborate, in 16 addition to my preclinical collaborations with 17 Latina American investigations -- these are clinical 18 studies that address clinical questions in 19 collaborative trials. And, in my opinion, it's been 20 the direct individual connections between people that 21 are the key to success in these kinds of efforts.</p> <p>22 And as far as potential collaborating</p>	<p>1 to thank the organizers for giving me the opportunity 2 to tell you a bit about NIH's development efforts and 3 support mechanisms for valley fever. Some of this 4 talk will be familiar to folks who attended 5 yesterday's workshop, but here I'll be diving more 6 deeply into NIH's support for the single indication. 7 Throughout the talk I'll be encouraging folks to reach 8 out to us. So, upfront I just want to let you know 9 that my email is my first name, dot, my last name 10 @NIH.gov. I have no disclosures.</p> <p>11 To get us all oriented, the mission of 12 the National Institute of Allergy and Infectious 13 Diseases, or NIAID, is to lead research to understand, 14 treat and prevent infectious, immunologic and allergic 15 diseases.</p> <p>16 Within NIAID, the Division of 17 Microbiology and Infectious Diseases, or DMID, has a 18 broad mandate supporting research for over 300 19 pathogens, including the coccidioidi species, which, 20 as Dr. Stevens just demonstrated to us, are the 21 causative agents of valley fever.</p> <p>22 To give an idea of the scope of NIAID's</p>
<p>Page 23</p> <p>1 sites, my opinion would be the best bet would be 2 Mexico, based on the number of cases that they have 3 there, the proximity to the United States, past 4 history of success in collaborative ventures with 5 Mexican investigators and clinicians, and because of 6 the existing ties already to American investigators. 7 And Rafael and Luis can address this to a greater 8 extent.</p> <p>9 So, with that, I'll conclude, and I'd 10 be happy to take any questions. And thank you for 11 your attention.</p> <p>12 SUSAN HOOVER: Thank you, Dr. Stevens. 13 And thanks again to John Farley, who's gotten us off 14 to a good start time-wise.</p> <p>15 Our next speaker discussing current 16 developments at NIAID is Erin Zeituni. Dr. Zeituni 17 has been a Preclinical Services Program Manager in the 18 Bacteriology and Mycology Branch at NIAID since 2016.</p> <p>19 DR. ERIN ZEITUNI: Thank you, Susan. 20 Can I do a quick sound check?</p> <p>21 SUSAN HOOVER: We hear you.</p> <p>22 DR. ERIN ZEITUNI: Perfect. I'd like</p>	<p>Page 25</p> <p>1 funding for valley fever, in 2019, \$10 million of 2 NIAID's budget went to support for coccidioidomycosis 3 research and development. Those funds were spread 4 across the product development area that is shown on 5 this slide, which spans basically research through to 6 clinical research on the path to regulatory approval.</p> <p>7 Today, I will be diving into the valley 8 fever specific portfolios of the various mechanisms 9 that NIAID leverages to support and de-risk product 10 development for valley fever. Taking a look at the 11 blue arrows at the bottom of the screen, folks in the 12 audience will be most familiar with NIAID's grants and 13 contracts mechanism, which are the main drivers of 14 NIAID's support for product development effort.</p> <p>15 However, we do recognize that the path to product 16 approval is long and can be difficult. And so DMID 17 has developed free services and resources for the 18 research and development communities to access. Those 19 include the Preclinical Services Program and the 20 clinical trial units, both of which I will highlight 21 today.</p> <p>22 In the interest of time, I have</p>

<p style="text-align: right;">Page 26</p> <p>1 restricted this talk to a discussion of product 2 development efforts, so I feel it's important to 3 mention that there is also a small but mighty 4 portfolio of basic researchers tackling the task of 5 improving our knowledge of the basic biology of 6 coccidioides, its response to hosts and the host 7 response to infection. We applaud their efforts in 8 this challenging arena and we encourage folks to 9 continue bringing their exciting ideas forward in 10 grant application.</p> <p>11 Shown on this slide, DMID supports a 12 robust grant portfolio of drugs and diagnostics 13 targeting valley fever. The drug developers 14 highlighted here have received a mixture of grant 15 funding and preclinical services over the years to 16 help support their antifungal development programs for 17 valley fever.</p> <p>18 Some utilize grants, such as Amplyx 19 Pharmaceuticals' Fosmanogepix Program, while others 20 utilize a mix of grants and preclinical services such 21 as Mycovia's VT-1598 program and Valley Fever 22 Solutions' Nikkomycin Program. And still others</p>	<p style="text-align: right;">Page 28</p> <p>1 Dr. Galgiani's live attenuated vaccine 2 uses a strain rendered avirulent by the deletion of 3 the CPS1 gene, an essential gene for serial 4 propagation in <i>C. posadasii</i>. Dr. Galgiani is working 5 with an industrial partner, Anivive Lifesciences, to 6 develop the vaccine further. The recombinant chimeric 7 polypeptide antigen vaccine developed by Dr. Wang 8 contains the most immunogenic fragments of four 9 previously identified coccidioides antigens as well as 10 multiple human T-cell epitopes, and it's formulated 11 with a glucan-chitin particle as an undulant delivery 12 vehicle. This vaccine is in the proof of concept 13 stage.</p> <p>14 To help us better understand the 15 challenges and gaps that are facing the endemic 16 vaccine research community, NIAID organized a workshop 17 in 2019 to engage this research community in a 18 discussion of vaccine strategies for endemic fungal 19 pathogens. Over the course of one and a half days, 20 over 100 people dove into the science of the latest 21 discoveries in this field and strove to identify 22 actionable steps to advance fungal vaccines.</p>
<p style="text-align: right;">Page 27</p> <p>1 utilize preclinical services alone such as F2G's 2 olorofim program. We'll be hearing from 3 representatives from several of these companies later 4 during the workshop.</p> <p>5 NIAID program staff can also release 6 program announcements or SBIR contract topics to 7 encourage applications in research areas of special 8 interest. We continue to emphasize valley fever 9 research and development in recent initiatives. 10 Through these mechanisms, this year NIAID funded 11 several investigator-initiated grants and SBIR 12 contracts supporting diagnostic programs targeting 13 endemic fungal pathogens, including the coccidioides 14 species.</p> <p>15 Coccidioidomycosis vaccine development 16 efforts have a long history of NIAID grant support 17 over the years, however, this field remains quite 18 challenging. Two NIAID-funded vaccine programs of 19 note are the live attenuated vaccine out of the 20 University of Arizona and the recombinant chimeric 21 polypeptide antigen vaccine out of the University of 22 Texas, San Antonio.</p>	<p style="text-align: right;">Page 29</p> <p>1 Exciting outcomes of the workshop 2 included expanding the field of investigators and 3 initiated new collaborations. Additionally, the 4 workshop confirmed the scientific gaps and challenges 5 that needed attention, so as identifying new antigens, 6 understanding correlates of protection and meaningful 7 biomarkers, strengthening preclinical and clinical 8 testing, and overcoming manufacturing hurdles 9 including (inaudible) optimization as well as 10 regulatory challenges.</p> <p>11 Our program staff was poised to move 12 forward incorporating what we had learned in the 13 workshop, and program officers were able to leverage 14 the positive outcomes of the workshop to develop a 15 targeted FY22 initiative that was recently approved by 16 DMID's counsel, moving it forward as a potential 17 funding opportunity.</p> <p>18 The coccidioidomycosis collaborative 19 research centers will aim to establish highly 20 collaborative multidisciplinary research teams to 21 conduct translational and clinical research for 22 improved diagnosis, treatment and prevention of valley</p>

<p style="text-align: right;">Page 30</p> <p>1 fever. The goal is for these multidisciplinary 2 centers to leverage unique resources and patient 3 populations from endemic regions to advance the field. 4 We are looking forward to seeing the valley fever 5 research community continue to expand and advance in 6 the coming years.</p> <p>7 Switching gears away from the 8 investigator-initiated grants and contracts, I'd like 9 to introduce you all to NIAID's Preclinical Services, 10 which are a suite of contracts designed to support 11 anti-infective product development. These free gap- 12 filling services are intended to lower the risk and 13 advance promising discoveries along the product 14 development pathway.</p> <p>15 Our mission is to keep products moving 16 forward, rather than have them stall due to 17 intermittent gaps in funding or access to resources. 18 these free services are available to innovators from 19 academia, nonprofit organizations, industry and 20 government, both domestic and foreign institutions may 21 apply, and applicants do not need to have NIH funding. 22 Because this support mechanism is</p>	<p style="text-align: right;">Page 32</p> <p>1 here.</p> <p>2 Through preclinical services, we offer 3 both a central nervous system infection model and a 4 pulmonary infection model for valley fever. In the 5 CNS model, the infecting inoculum is delivered 6 intracranially to ICR mice who are then treated two 7 days later for durations of either seven days to 8 assess the impact of treatment on the fungal burden of 9 select tissues, or treated for 14 days followed by a 10 14 or 28-day off therapy monitoring period to observe 11 the impact on survival.</p> <p>12 The pulmonary model has several key 13 differences. The infecting inoculum is delivered to 14 the lungs of ICR mice and treatment is started five 15 days later. The fungal burden assessment runs largely 16 the same from that point onward, whereas the survival 17 arm of the study has a shorter treatment duration than 18 the CNS model but with a similar off-therapy 19 monitoring period. A drug's characteristics will help 20 determine which model to pursue.</p> <p>21 In addition to efficacy assessment, 22 NIAID's preclinical services also offer a suite of</p>
<p style="text-align: right;">Page 31</p> <p>1 intended to quickly fill discrete gaps in product 2 development programs and keep them moving forward, 3 there's a simplified request process allowing access 4 year-round.</p> <p>5 Focusing on valley fever, I manage a 6 suite of in vitro and in vivo efficacy studies -- 7 services that provide supportive data to antifungal 8 drug development programs, including those targeting 9 coccidioidomycosis. Because coccidioides require BSL3 10 facilities, accessing efficacy evaluations can be a 11 rate limiting step, and we find that it frequently is 12 not on the radar of early development programs 13 developing broad spectrum antifungals. We offer these 14 services to ensure that promising antifungals have 15 pass (inaudible) to assess their activity.</p> <p>16 To give a flavor of our scale of our 17 services since 2015, our contractors at the University 18 of Texas Health Science Center in San Antonio have 19 performed MIC testing against coccidioides for 25 20 compounds from 18 institutions, and they have 21 evaluated in vivo efficacy for five institutions and 22 two valley fever infection models that are illustrated</p>	<p style="text-align: right;">Page 33</p> <p>1 preclinical studies to support antifungal drug and 2 vaccine programs at multiple stages of development. 3 These services include chemistry and manufacturing, 4 including GMP manufacturing, toxicology and 5 pharmacokinetics, rapid ADMET and pharmacokinetics 6 screening, product development planning and assistance 7 with IND documentation, vaccine testing, and vaccine 8 and biologic manufacturing services.</p> <p>9 So, if we're thinking back to the in 10 vivo efficacy models for valley fever that I mentioned 11 on the previous slide, when investigators are 12 preparing to test their products in this rather tough 13 model under BSL3 conditions, they need to have access 14 to a robust preliminary data package to support that 15 study. This includes sufficient compound for key 16 study arms with 7-14 days of dosing, MIC testing 17 against the strains used in the models, and 18 understanding of the pharmacokinetics and distribution 19 of their drugs in the blood, brain and/or lungs to 20 help them select their doses, and the knowledge that 21 their drugs is tolerated in ICR mice for the plan 22 dosing schedule and duration.</p>

<p style="text-align: right;">Page 34</p> <p>1 So, for those of you in the audience 2 who are already making this checklist in your head, 3 please know that although our preclinical services are 4 intended to be gap filling, we do understand that 5 there can be more than one gap in a program. I 6 encourage you to reach out to us and tell us about 7 your antifungal programs and your gap. And I'd like 8 to state that once again for emphasis. Please do 9 reach out to us.</p> <p>10 F2G has kindly given me permission to 11 describe our interactions has an illustrative example 12 of NIAID's... Oops, where are we? There we go. As 13 NIAID's interaction with drug developers. Starting in 14 the box on the left, in an introductory call between 15 NIAID and F2G, we described our in vivo efficacy 16 services in general to the F2G team and mentioned that 17 we had a single study slot available in our 18 coccidioides in vivo testing task order. At that 19 time, F2G had shown in silico and in vitro that their 20 advanced agent, Olorofim, had activity against 21 coccidioides, and we went on to verify that through an 22 expanded MIC panel against C. immitis and C.</p>	<p style="text-align: right;">Page 36</p> <p>1 The primary objectives of this study 2 are to determine the safety of single ascending oral 3 doses of VT-1598 in healthy adult subjects in a fasted 4 state and to determine the safety of a single oral 5 dose of VT-1598 in healthy adult subjects in a fed 6 state.</p> <p>7 In addition to the Phase 1 clinical 8 trial units, NIAID's Infectious Disease Clinical 9 Research Consortium, previously the Vaccine Treatments 10 and Evaluation Unit, have also been leveraged to 11 support clinical studies in valley fever. An 12 observational study of up to a thousand individuals 13 aged greater than or equal to 14 years has the 14 objective of assessing the prevalence of primary 15 pulmonary coccidioidomycosis or PPC in subjects with 16 community-acquired pneumonia or CAP in 17 coccidioidomycosis endemic areas.</p> <p>18 Step one of the study is to examine the 19 prevalence of PPC among individuals presenting with 20 CAP within 28 days of symptom onset. Step two of the 21 study is to follow individuals diagnosed with PPC for 22 up to 24 months to establish the clinical course,</p>
<p style="text-align: right;">Page 35</p> <p>1 posadasii at our contracting site at the University of 2 Texas Health Sciences Center in San Antonio.</p> <p>3 With that confirmation, we embarked on 4 the in vivo assessment of Olorofim in the CNS 5 infection model where significant protection and 6 fungal burden reduction was observed in that model 7 compared to untreated controls. Results of the 8 efficacy model were published and as we will hear 9 later today, F2G is exploring clinical use of Olorofim 10 for coccidioidomycosis. This is a powerful example of 11 the potential impact of a simple conversation. If you 12 have a promising antifungal agent, please do contact 13 us and we will be happy to hear from you.</p> <p>14 Additional free services include our 15 clinical trial units, such as our Phase 1 units. 16 These contracts provide Phase 1 trials at no cost to 17 the requester. NIAID sponsors the trial and holds the 18 IND. Mycovia's VT-1598 is a novel antifungal compound 19 with activity against coccidioides species. Through 20 our Phase 1 clinical trial units, VT-1598's single 21 ascending dose is examining the safety of its 22 administration to 48 healthy adults aged 18-45 years.</p>	<p style="text-align: right;">Page 37</p> <p>1 identify predictors of the clinical course and 2 evaluate the response to prescribed antifungal therapy 3 versus no antifungal therapy. This observational 4 study is enrolling and we're looking forward to 5 producing perfective data on the prevalence of PPC in 6 CAP and the management of early PPC at the earliest 7 point of treatment.</p> <p>8 I hope that this presentation has 9 helped provide a clear picture of the various 10 mechanisms that NIAID is leveraging to support product 11 development targeting valley fever. Management of the 12 portfolios and mechanisms described in this 13 presentation are a team effort and I'd like to 14 acknowledge the members of the Bacteriology and 15 Mycology branch who helped with the valley fever 16 effort. They are all listed here on the slide. My 17 email is provided at the top of the slide. Please 18 reach out to me if you have any questions. I hope to 19 hear from you. Thank you.</p> <p>20 SUSAN HOOVER: Thank you, Dr. Zeituni. 21 Our last talk before our morning break is Dr. Lisa 22 Shubitz talking about animal models of</p>

<p style="text-align: right;">Page 38</p> <p>1 coccidioidomycosis. Dr. Shubitz is a research 2 scientist at the Valley Fever Center for Excellence, 3 has been working on cocci since 1996. 4 DR. LISA SHUBITZ: Good morning. And I 5 was asked -- first of all, I'm very honored to be a 6 part of this workshop today and asked to -- have been 7 asked to speak to you. And this is going to be a bit 8 redundant with the last talk, unfortunately. This is 9 what I was asked to talk about, but it's not going to 10 be extensively -- it's not going to go extensively 11 past what Erin already gave you. 12 So, I'm going to talk a little bit 13 about animal models of coccidioidomycosis -- as soon 14 as I figure out how to move the slides. All right. 15 So, it's already been spoken about that cocci is a 16 biosafety level 3 pathogen, in that in order to do 17 animal work with coccidioids you have to have animal 18 biosafety level 3 facilities. And in addition, you 19 either need to have support of a biosafety level 3 20 micology laboratory also that can produce your 21 organisms or you need to have a relationship with 22 someone who can ship them to you.</p>	<p style="text-align: right;">Page 40</p> <p>1 look at it. 2 And in the lower right-hand corner is a 3 photograph of a class III biosafety cabinet. We've 4 actually had one in place at our institution since 5 1998 and it has two workstations in it which makes the 6 work more efficient for packing cages and animal 7 transport. But this is -- I don't think everyone has 8 a class III cabinet in order to be able to do this 9 work, and it can be done other ways, but it's a nice 10 safety feature. 11 So, mice are mostly what is used. They 12 constitute the vast majority of the animals that are 13 used in research and preclinical efficacy studies of 14 antifungal drug candidates for coccidioides. The 15 advantages of mice is that there are very well- 16 established cocci infection models in mice that have 17 been used for over 70 years -- the literature goes 18 back into the 1950s. 19 They're small and easy to handle in 20 statistically significant number at animal biosafety 21 level 3, and that is indeed a factor. It's very easy 22 to put a small cage of mice into a class III biosafety</p>
<p style="text-align: right;">Page 39</p> <p>1 So, the pathogen is a significant 2 aerosol risk to personnel, which is why you have to be 3 working with this animal bio safety level 3. It's not 4 really transmissible from one animal to another but 5 you could give it to yourself or the other workers in 6 your laboratory while you're infecting your animals. 7 Consequently, this requires that all of your personnel 8 be properly trained at biosafety level 3 and at 9 handling animals at biosafety level 3, and it requires 10 that you have at least a class II biosafety cabinet 11 with some extra PPE such as N-95 for protection from 12 aerosols, or you could have a class III biosafety 13 cabinet for intranasal infections. And intranasal 14 infections carry the greatest risk of infecting 15 workers, but there are small aerosols that can be 16 created even just squirting things out of needles. 17 The guidelines for setting up an animal 18 biosafety level 3 laboratory are published in the 19 Biosafety in Microbiological and Biomedical 20 Laboratories, which is a CDC publication. And they 21 used to mail it to you but now it's actually just 22 available on their website as a PDF and you can go</p>	<p style="text-align: right;">Page 41</p> <p>1 cabinet or a class II biosafety cabinet. It becomes a 2 little bit more challenging when you're using larger 3 animals. You can also involve statistically 4 significant numbers of the animals because they're 5 little. 6 There are a wide variety of strains for 7 drug studies. Outbred mice or the ITR mouse, which is 8 an inbred swift that Erin was talking about, are 9 relatively inexpensive and they're used very commonly 10 for drug studies. But if you're interested in effects 11 of drug in the face of infections that may be more 12 challenging due to underlying conditions in a human 13 being, there are a lot of genetically engineered mice 14 available now that mimic metabolic or immunologic 15 system defects in mice that you can purchase to use. 16 The drawbacks of mice are that the 17 pharmacokinetics of the drugs in mice may differ 18 significantly from what's seen in humans, and that 19 means that you actually need to perform -- or you may 20 need to perform some PK in mice to understand how to 21 use them as a model. 22 The other drawback is that coccidioides</p>

<p style="text-align: right;">Page 42</p> <p>1 progresses pretty rapidly in mice, whereas even an 2 immuno-deficient human, you know, may have the disease 3 for two or three weeks before they even show up in 4 your office because they're sick. In two or three 5 weeks, the laboratory infected mouse is typically 6 dead.</p> <p>7 So, I'm going to talk a little bit 8 about routes of administration, which Erin described 9 some of already. But the pulmonary route of 10 administration is the most common. This is the way 11 the infection gets into the human host naturally, and 12 it makes sense to put it into the lungs. This also 13 carries the greatest aerosol risk.</p> <p>14 So, it can be administered intranasally 15 by insufflation of a saline suspension -- with the 16 opportunity in a saline suspension using a pipette, 17 which is very simple. And it's not 100 percent. 18 You're giving this to an anesthetized animal. I think 19 I actually have a little picture here. No, I don't. 20 It's on another slide. Use a pipette, let them inhale 21 it through their nose while they're anesthetized. But 22 some of it goes down the esophagus instead of the</p>	<p style="text-align: right;">Page 44</p> <p>1 infection, which provides a rapid widespread model of 2 dissemination very early on that doesn't go through 3 the lungs to get to a disseminated state, and it's a 4 little bit technically challenging. Intraperitoneal 5 gives you dissemination but Lung Fungal Burden is a 6 common readout because it typically goes to the lungs 7 really easily. There is an intrathecal model for CNS 8 infection in mice. It is technically challenging, but 9 it is published. And then intracerebral infection 10 with (inaudible) also produces a CNS infection.</p> <p>11 So, here's a picture of the mouse 12 being infected. So, 50-100 spores of a common 13 virulent laboratory strain in 30-50 microliters of 14 isotonic saline is being administered to this 15 anesthetized animal. This is in the class III 16 cabinet. Just using a pipette and applying this drop 17 (inaudible) to the nares and waiting for the animal to 18 inhale the suspension until the suspension's been 19 completely administered. We did this under Ketamine- 20 Xylazine anesthesia, which produces a nice smooth 21 anesthesia that lasts long enough to perform this in 22 the equipment that I have. I think other people do</p>
<p style="text-align: right;">Page 43</p> <p>1 airways. Much of it may be tracked in the upper 2 airways, the nasal passages, the upper bronchi. But 3 some of it definitely gets delivered to the lower 4 airways where it sets up infection. And this is an 5 affective and common way to infect mice.</p> <p>6 So, you can give it intratracheally. 7 There are methods of doing this. I think they're a 8 little bit more challenging, at least in a class III 9 cabinet, which is what I have, where you anesthetize 10 the animals or you could deliver this with a pipette 11 to the trachea and bypass the nasal passages. It can 12 be done surgically, but I don't think anyone's doing 13 that in mice.</p> <p>14 They could be exposed by aerosol in 15 chambers, but this carries very high risk of aerosol 16 infection and I don't actually know anyone who's doing 17 it. But if you're more interested in nebulized spores 18 with well-distributed infections that go deep into the 19 lungs, this might be something to consider. For a 20 model for a drug, I'm not sure this is really worth 21 pursuing.</p> <p>22 Other methods are intravenous</p>	<p style="text-align: right;">Page 45</p> <p>1 this with some kind of inhaled anesthetic, but I find 2 that the Ketamine-Xylazine works pretty well because 3 it lasts a little bit longer.</p> <p>4 And in talking about this pulmonary 5 model, it takes four days, four to five days to reach 6 the first generation of spread of this infection, from 7 the time they inhale arthroconidia until the first 8 round of endospores are released to form new 9 spherules, which increase your infection by, 10 approximately one-hundredfold, requires 96 hours.</p> <p>11 So, if you look in the literature, some 12 studies utilizing mice, treatment had begun at 48 13 hours after pulmonary infection, which gets your drug 14 onboard by the time this first round of spherules 15 rupture. But we typically start to treat this 16 infection at 120 hours, which is day five, and this 17 gives time for the infection to become established. 18 And while we can't really mimic what happens in the 19 real world using a mouse model, which is that people 20 do not show up for treatment until they're ill, it is 21 more similar to a human seeking medical care because 22 you're not treating just this developing first round</p>

<p style="text-align: right;">Page 46</p> <p>1 of spherules and endospores -- you've actually got 2 establishment of the infection in the animal. 3 In untreated mice, in 2-3 weeks, 4 they're moribund. So, between 14 and usually 23-25 5 days, your mice have died if they're not being 6 treated. And it's important to know your model to 7 prevent cage deaths. And mice with cocci -- I guess 8 sick mice, in general, are kind of generically this 9 way -- but they get thin and they can lose weight very 10 quickly. They develop a hunched posture and ruffled 11 fur, though how ruffled it looks is dependent upon the 12 mouse strain that you're using. They become 13 tachypneic if you observe them just sitting in the 14 cage with their little noses down in the shavings. 15 And they get weak. If you pick them up, they feel 16 weak. They don't feel like a normal mouse. And 17 they're dehydrated based on skin turgor. If you pinch 18 the skin on the back of their neck, it doesn't return 19 to its normal position. 20 When you estimate that the mice won't 21 survive another 24 hours, we euthanize them. We don't 22 wait for them to die in the cage. For one thing, the</p>	<p style="text-align: right;">Page 48</p> <p>1 It is a 2-3 week infection model, which 2 is similar to the intranasal and intravenous, and what 3 you see in these is granulomas of the cranial 4 mesentery, spleen and liver with dissemination to the 5 lungs. It's very prominent in a miliary pattern. 6 The intracerebral and intrathecal 7 administration routes produce meningitis models. And 8 the intrathecal is put into the mouse in the 9 (inaudible) thoracic upper lumbar area. The 10 intracerebral goes directly into the brain but both 11 models actually produce meningitis and a 12 meningomyelitis, so it goes up and down the spinal 13 cord. You find the organisms in the cord and in the 14 brain regardless of which method that you use. 15 Clinical signs occur in these mice in 16 6-8 days post infection and your deaths usually start 17 by day eight. The clinical signs are paresis, 18 paralysis, ataxia, circling, head tilt, seizures and 19 obtundation. And within my experience, these animals 20 need to be evaluated twice a day for animal welfare 21 purposes. Because once the clinical signs begin, the 22 animals may progress very rapidly and they'll be dead</p>
<p style="text-align: right;">Page 47</p> <p>1 main thing we assess in these animals is fungal 2 burdens, and I prefer not to have to just pick up dead 3 mice out of the cage and cut the lungs out of them. 4 With intravenous infections, these are 5 something that I have not performed, so this is based 6 on literature. But doses of, approximately, 50 spores 7 intravenously produces deaths after day 12, according 8 to Clemons. And in published studies using 9 intravenous infections, treatment is indeed usually 10 instituted within 48 hours post infection. If there's 11 more updated information on that, I don't actually 12 have it. 13 Intraperitoneal infection is something 14 that carries a little bit less aerosol risk than an 15 intranasal infection. It usually requires more 16 arthroconidia to initiate the infection by this route 17 but it's very reliable. It is technically easy to 18 perform at biosafety level 3 compared to an intranasal 19 infection. The animals do not have to be 20 anesthetized. And this can be easily accomplished in 21 a class II cabinet without probably a lot of other 22 protective -- other protective gear.</p>	<p style="text-align: right;">Page 49</p> <p>1 in 24 hours. 2 With this model you generally institute 3 treatment within 48 hours because of how rapidly this 4 progresses. And the assessment is either fungal 5 burden or survival. And I recommend assessing lungs 6 and spleens, not just your brain and spinal cord 7 because this very easily goes to both of those places. 8 So, in terms of assessing mouse models 9 after treatment, survival is one thing that can be 10 assessed. You treat them for a given period of time 11 and then stop your treatment and see if they die. 12 Organ fungal burdens at a specified 13 time after stopping treatment are probably the more 14 common assessment, and organ fungal burdens may be 15 your primary measure. There is the question of 16 eradication versus reduction in colony-forming units. 17 Many of the antifungal candidates we have do not 18 eradicate the infection, so often you're looking for 19 excellent reduction in fungal burden compared to your 20 controls. 21 We quantitate colony-forming units or 22 CFU by tenfold serial dilutions of homogenized</p>

<p style="text-align: right;">Page 50</p> <p>1 tissues, which are usually limited to the lung and 2 spleen. If you're doing CNS models, you're maybe 3 doing spinal cord and brain as well. And you can also 4 qualitatively assess dissemination by incubating whole 5 organs on plates, which is a reasonable approach if 6 you've got some experience with your models and you 7 gave an intranasal infection and you expect control, 8 and you're not that interested in whether there are 9 three organisms in the spleen or ten, but you just 10 want to know if it's there at all. Body weight is a 11 really good measure and indicator of progression of 12 infection, even before your other clinical signs 13 become visible.</p> <p>14 The rabbit can be a very reliable model 15 of coccidioidal meningitis and arteritis that is more 16 similar to the disease in humans than what we can 17 produce in mice. The infection is performed 18 cisternally and the size of the animal allows some 19 serial cisternal sampling of CSF, so you can get some 20 intermediate measures in a rabbit that you cannot in 21 mice.</p> <p>22 The post-mortem analysis would include</p>	<p style="text-align: right;">Page 52</p> <p>1 nebulization model that produced very good infection. 2 It seems that most drugs at this stage 3 would probably be implemented in some kind of a human 4 trial and not ever go through a nonhuman primate. But 5 if you have a product that you really think you'd like 6 to put into a primate, there could be some 7 opportunities to treat naturally infected nonhuman 8 primates that are in primate centers within endemic 9 areas.</p> <p>10 From some small amount of personal 11 experience, there can be some challenges with 12 administering drugs daily to nonhuman primates and 13 also monitoring because the animals require anesthesia 14 in most cases.</p> <p>15 I'm going to talk only briefly about 16 naturally infected dogs because I think they're a 17 rather interesting preclinical assessment model for 18 drug efficacy. In southern Arizona, where I work, we 19 have a very high caseload and it's actually really not 20 difficult to enroll cases. And we worked with a 21 company with one of the VT drugs in doing a clinical 22 assessment of their drug in naturally infected dogs.</p>
<p style="text-align: right;">Page 51</p> <p>1 histopathology, you can do fungal burden of the spinal 2 cord and the brain, you can evaluate cerebral spinal 3 fluid, and this has been reported to be a good model 4 for humans.</p> <p>5 Some of the drawbacks of this is you 6 need to understand the PK of your drug in this 7 species, which may not be a routine part of what 8 you're producing. And there's an increased cost of 9 animals, the labor to handle them and take care of 10 them, and the cost of housing them. So, you end up 11 with fewer animals and you might end up with less 12 robust statistics. Your facilities need to be able to 13 manage the larger animal models at animal biosafety 14 level 3.</p> <p>15 I include this slide on nonhuman 16 primates because they're possible, though I don't see 17 that most people would be interested in using them. 18 But they could be used experimentally but it would be 19 extremely expensive, and there are other reasons not 20 to. I would recommend an intratracheal infection with 21 arthroconidial suspension that's been administered 22 using a nebulizer after having worked out this dog</p>	<p style="text-align: right;">Page 53</p> <p>1 And unlike nonhuman primates, they usually do not 2 require anesthesia to monitor.</p> <p>3 And it is possible to assess 4 improvement in pulmonary disease within 30-60 days of 5 treatment using radiography, serology and serum 6 chemistries and CBCs. These are really easy to 7 collect on client-owned dogs. And the owners are 8 actually extremely grateful for the opportunity to get 9 a potential treatment for their animal, and they're 10 really dedicated. We get very low dropout rates in 11 dog studies -- just dog studies, in general.</p> <p>12 The drawbacks to this, of course, are 13 cost, the time it takes to perform this because you do 14 have to enroll animals and it's, you know, similar to 15 enrolling in human clinical trials -- they come in 16 spurts and fits. And you may not end up with 17 statistically significant numbers that would help 18 drive your development, and you could end up with 19 primarily descriptive data from such a study, but 20 maybe it would be valuable to you.</p> <p>21 The potential advantages of this model 22 are that it does involve naturally occurring disease</p>

<p style="text-align: right;">Page 54</p> <p>1 in a model that's already sick, in a species that has 2 a rate and range of disease that's pretty similar to 3 humans. And the dog is a common PK and toxicology 4 species, so you may know exactly what you need to give 5 them in terms of dose. And oral administration to 6 dogs is actually pretty easy.</p> <p>7 So, in summary, the mouse model is the 8 workhorse of the preclinical testing of antifungal 9 drug candidates because they're small, the models are 10 really well-developed and these studies are very cost 11 effective.</p> <p>12 If you need a more advanced 13 meningitis/arteritis model, the rabbit can be an 14 option for you. The drawbacks being that you need 15 some technical expertise, it will cost more, and you 16 may have to have extra facilities to do this. And 17 then there are some larger animal models, both 18 naturally infected and laboratory-induced that exist 19 that you would need to weigh the benefits of doing 20 that for your drug.</p> <p>21 Thank you very much for your time. I 22 really appreciated the opportunity to speak to you.</p>	<p style="text-align: right;">Page 56</p> <p>1 Administration for hosing this workshop and allowing 2 me to be a part of it. It's a privilege to be able to 3 speak on behalf of the Valley Fever patient community. 4 Let me get my slides going. There it goes.</p> <p>5 So, I will be sharing some of my 6 personal experience as a patient, as well as knowledge 7 I have gained through countless interactions with 8 other patients to provide a perspective on the 9 difficulty many patients face in fighting valley 10 fever. I will also share some of the work being done 11 at the Valley Fever Institute to support patients 12 using a 360-degree care model, and the opportunity and 13 importance of patients in efforts to develop, test and 14 validate new drugs.</p> <p>15 So, I could easily spend 15 minutes 16 just sharing my valley fever journey, and for the sake 17 of time, I'll share the aspects that are relevant to 18 today's topic. My story is very similar to the 19 experience many patients have with disseminated cocci. 20 My valley fever story began with a headache on January 21 1st of 2012. I was diagnosed with a sinus infection, 22 and after two trips to the urgent care and two</p>
<p style="text-align: right;">Page 55</p> <p>1 LANLING ZOU: Hello? Everybody can 2 hear me?</p> <p>3 SUSAN HOOVER: Yes.</p> <p>4 LANLING ZOU: Oh, okay. Hi. This is 5 Lanling Zou. I'm the co-moderator. I just want to 6 thank everybody, all the speakers this morning for 7 their excellent presentations. They're very 8 comprehensive and informative. I think it's time for 9 a short break. Please rejoin us at 12:20 for the next 10 talk. All right, see you then.</p> <p>11 (Break)</p> <p>12 LANLING ZOU: Welcome back. It is my 13 pleasure to introduce our next speaker, Mr. Rob 14 Purdie. He's currently the Patient and Program 15 Development Coordinator at the Valley Fever Institute. 16 He's going to speak about patient oriented clinical 17 trial design. Bob, please take it away.</p> <p>18 ROB PURDIE: Thank you. Can everybody 19 hear me okay?</p> <p>20 SUSAN HOOVER: Yeah. Yes.</p> <p>21 ROB PURDIE: Oh, great. Thank you. 22 Good morning. I'd like to thank the Food & Drug</p>	<p style="text-align: right;">Page 57</p> <p>1 unnecessary rounds of antibiotics, I saw an ENT 2 specialist who confirmed I did not have a sinus 3 infection.</p> <p>4 My next diagnosis was cluster 5 headaches, and eventually I developed other symptoms 6 including double vision, which brought me to the 7 Emergency Department at Kern Medical in Bakersfield, 8 which is now home to the Valley Fever Institute, and I 9 was admitted to the hospital on February 5th, where 10 the doctors told me I had cocci meningitis. The 11 nearly six weeks it took to be diagnosed with cocci 12 seemed like a long time, and for many illnesses that 13 would be a long time, but I've talked to countless 14 patients who spent months seeking a diagnosis for 15 their valley fever, so I feel I was extremely lucky to 16 be diagnosed in six weeks.</p> <p>17 For most people, valley fever is an 18 inconvenient lingering flu-like illness with extreme 19 fatigue. Disseminated coccidioidomycosis is a 20 devastating life sentence. And if you're lucky, 21 you're able to have a functional life. One of my 22 personal goals as part of public education efforts is</p>

<p style="text-align: right;">Page 58</p> <p>1 to better communicate the difference in disease 2 severity and the impact that cocci can have. 3 I was started on 1000 milligrams of 4 Fluconazole and discharged from my hospital on 5 February 18th of 2012. I was readmitted to the 6 hospital on February 19th with bilateral plural 7 effusions and I remained there until I was discharged 8 on March 5th. When I was discharged in March, I'd 9 lost 70 pounds and three months of my life and my 10 headache was still there. 11 By mid-May, my headache was almost 12 gone, I had no energy, no appetite and I was 13 constantly thirsty. I also had the cracked lips 14 common with patients on high-dose Fluconazole. I felt 15 like I was living life with a water bottle in one hand 16 and ChapStick in the other. 17 In October of 2012, I was readmitted to 18 Kern Medical because I clinically failed Fluconazole, 19 which means that my doctors failed to see an 20 improvement in my clinical endpoints after six months 21 of use, even though my drug levels were in the 22 therapeutic range. I was discharged three days later</p>	<p style="text-align: right;">Page 60</p> <p>1 with those precautions I was diagnosed with squamous 2 cell carcinoma. 3 After my second diagnosis, I failed 4 Voriconazole due to the skin cancer, and I was started 5 on Posaconazole. Even though I'm no longer on the 6 Voriconazole, I still have to limit my time outdoors. 7 Summers at the beach or spending the day by the pool 8 are all very popular activities in Bakersfield but I'm 9 not able to participate due to my skin cancer. I 10 still require quarterly follow-ups with a 11 dermatologist and I've had four more squamous cell 12 carcinomas removed, one of which required 13 reconstructive surgery on my ear. 14 The side effects I experienced with 15 Posaconazole, while not as medically concerning, do 16 have an impact on my life. I experience frequent 17 nosebleeds but they're usually very minor, and profuse 18 sweating, which makes me self-conscious and has caused 19 quite a bit of concern at some of the events I've 20 attended. And even with my improved quality of life, 21 the impact of the medications are just beneath the 22 surface.</p>
<p style="text-align: right;">Page 59</p> <p>1 and started on 600 milligrams of Intraconazole. I 2 clinically failed Intraconazole as well, and on 3 January 15th of 2013, I was started on 450 milligrams 4 of Voriconazole. By summer of 2013, I clinically 5 failed Voriconazole as monotherapy and IT Amphotericin 6 B was recommended to be added to my treatment. I 7 began my IT Ampho treatments on December 3rd of 2013. 8 So, not all failures are the same. 9 Some failures are due to the side effects of the drug, 10 and my Ampho treatments continued twice a week until 11 June of 2014. On June 18th of 2014, after my 12 treatment, I had lower body numbness and trouble 13 walking. At my next treatment, my dose was cut in 14 half, but I had the same problem. 15 My treatments were moved to once a week 16 at the lower dose and the side effects were still 17 present but manageable. My health improved and 18 treatments eventually moved to once a month. The 19 Voriconazole combination therapy was effective in 20 controlling my disease, but it came at a cost. As 21 soon as I started taking the Voriconazole, I took 22 precautions to protect my skin from the sun but even</p>	<p style="text-align: right;">Page 61</p> <p>1 The impact on the quality of life from 2 side effects can influence patient adherence to 3 treatment. Patients with non-complicated disease who 4 experience severe side effects may discontinue 5 treatment, and patients with severe disease may not 6 adhere to care well. I've spoken to several otherwise 7 intelligence patients who discontinued their treatment 8 just because the side effects had a greater impact on 9 their quality of life than their disease. 10 The azoles used to treat valley fever 11 are used off label and at higher doses than they were 12 approved for. Because of this, patients experienced 13 more extreme side effects. When a patient goes to Dr. 14 Google to find out information about how they're 15 feeling, many of the side effects that they say 16 they're experiencing are listed as reasons to stop 17 taking the drug and talk to their doctor. 18 Patients and their families need more 19 than awareness information about valley fever. 20 Knowing the likely side effects of the drugs and the 21 importance of continuing treatment can affect whether 22 a patient follows treatment guidelines.</p>

<p style="text-align: right;">Page 62</p> <p>1 Before a patient is treated with 2 Amphotericin, they are given a cocktail of medications 3 to control the side effects of the drug. When I'm 4 given IT Ampho, I become almost instantly nauseated 5 and I can actually feel my body react as the drug 6 spreads and I become violently ill. Luckily, I have 7 one bad day every ten weeks. Some patients need the 8 drug two or more times a week. For those patients, 9 there are no good days. These patients may skip 10 treatments due to the side effects of the drug and 11 many of these patients experience other difficulties 12 due to the severity of their disease.</p> <p>13 The burden of valley fever can be 14 broken down into direct and indirect costs. The 15 direct cost of the disease can be calculated pretty 16 easily and estimating some indirect cost such as lost 17 earnings are a little bit more difficult. But how do 18 you calculate the emotional cost of deteriorating 19 relationships with your family and friends, or the 20 result of the isolation and depression which are, 21 unfortunately, too common. Eight years later, I'm 22 still battling with these things.</p>	<p style="text-align: right;">Page 64</p> <p>1 begin to address the socioeconomic impact of cocci. 2 With the opening of the new Valley Fever Institute, 3 we're able to advance our goal of moving to a 360- 4 degree care model for our patients. We're adding 5 social and support services in addition to clinical 6 care.</p> <p>7 We are a teaching, treatment and 8 research facility and our mission is to improve 9 patient care, promote education and awareness, and 10 conduct research to benefit our community, and our 11 research team is growing. It includes six physicians, 12 a clinical pharmacist, a research nurse, many research 13 assistants, and we're adding an infectious disease 14 fellow in 2021.</p> <p>15 At the Valley Fever Institute we have 16 the largest population of valley fever patients and 17 many have consented to contact for future research. 18 In addition to providing a research source, our 19 patients have provided our doctors with experience in 20 treating severe cocci that they're able to share 21 through CME and other educational events. In 22 addition, our experts share their experience with</p>
<p style="text-align: right;">Page 63</p> <p>1 The impact of cocci on quality of life 2 is just as important to patients as the CF titer is to 3 most physicians. For many of these patients, the 4 quality of their lives have been reduced to a point 5 where they're unable to survive independently, and 6 many are dependent on government assistance of some 7 type. There have been multiple times over the course 8 of my illness that my family relied on assistance 9 programs, and my family is still recovering from the 10 finance destruction of chronic illness now.</p> <p>11 So, the Valley Fever Institute at Kern 12 medical was established in 2015, and part of our 13 mission is to share the knowledge accumulated by our 14 doctors in diagnosing and treating valley fever. More 15 than 1,500 patients are treated by the Valley Fever 16 Institute each year, many of us with severe forms of 17 the disease.</p> <p>18 Our coffee clinic sees over 200 19 patients a month, administers approximately 90 IV 20 infusions of Amphotericin and 40 intrathecal 21 inspections. Importantly, the Valley Fever Institute 22 is moving beyond clinical treatment of patients to</p>	<p style="text-align: right;">Page 65</p> <p>1 unique and difficult cases through published case 2 studies in academic journals and infectious disease 3 conferences.</p> <p>4 The patient program coordinator role, 5 which I occupy, was established to address the 6 difficulties faced by our patient population, provide 7 education and awareness of valley fever to the public 8 as well as provide information and resources to 9 patients.</p> <p>10 Cocci is a disease that has a 11 disproportionate impact on the poor and marginalized 12 members of our community. As a patient, I have a 13 unique understanding of our other patients, which 14 enhances the institute's ability to understand the 15 patient perspective.</p> <p>16 I still vividly remember my first 17 appointment at a cocci clinic. Speaking with other 18 valley fever patients in the waiting room, I realized 19 that in spite of everything my family had been through 20 and we were still facing, we were very lucky. 21 Speaking to patients, especially ones recently 22 diagnosed with disseminated disease, being able to</p>

<p style="text-align: right;">Page 66</p> <p>1 offer hope and encouragement is the most rewarding 2 thing I've ever done. 3 Working with the valley fever community 4 and those fighting valley fever has given me a new 5 purpose and energy and I've had a new opportunity to 6 work with the doctors at the Valley Fever Institute 7 who I credit with saving my life. 8 Patients are concerned first about how 9 they feel, and a distant second about how the disease 10 is improving. If you ask a patient how they feel, I 11 don't know any one of them that's going to tell you 12 that their CF titer hurt too bad to go to work, or 13 they missed class today because their white blood cell 14 count was elevated. The impact of the disease and its 15 treatment on the lives of patients cannot be fully 16 assessed by calculating hospitalization costs or 17 reviewing patient records. 18 The use of patient-reported outcome 19 measures provides an opportunity to record and 20 evaluate the patient's self-assessed health or quality 21 of life. The loss of quality of life here is 22 substantial for patients who suffer from the most</p>	<p style="text-align: right;">Page 68</p> <p>1 For patients newly diagnosed with 2 cocci, treatment will be different from any illness 3 they have ever had before. Patients who are used to a 4 course of antibiotics or some over-the-counter 5 medications for common infections are surprised to 6 learn that even for uncomplicated disease, 3-6 months 7 of medication or more is required. 8 The expectation that recovering from 9 cocci will be like recovering from flu is quickly 10 destroyed. However, we have the same treatment goals 11 and expectations for cocci as any other illness. We 12 want medications to resolve the disease and remove any 13 impact of it from our lives. Patients are very 14 concerned about the cost of medication. The out-of- 15 pocket cost is the only cost that matters to us 16 because that's what determines if we can afford it. 17 For some drugs we must get special approval from our 18 insurance companies, which is not always easy or 19 approved. 20 Patients may also require the use of 21 patient assistant programs to get the medication they 22 need, and the more complicated and restrictive these</p>
<p style="text-align: right;">Page 67</p> <p>1 severe cases. There's been a disconnect between the 2 clinical aspects of treating valley fever and the 3 quality of life experience by patients that's 4 beginning to narrow. 5 As a valley fever patient, I've been 6 able to communicate with patients in a different way 7 than a researcher or clinician would. My interaction 8 with our patients as well as valley fever patients 9 nationwide provide insights that benefit the patients 10 as well as our doctors and provides a foundation for 11 improved treatment and research. 12 The patient population at the Valley 13 Fever institute is a resource that can be used for 14 research into health-related quality of life. Current 15 research at the Valley Fever Institute utilizes 16 several different scoring systems to evaluate patient- 17 reported outcomes for our research. And I'm very 18 excited to say that along with our Psychiatry 19 Department, our doctors are conducting research into 20 correlations between cocci and depression, and we're 21 hoping to expand on these efforts in future research 22 projects.</p>	<p style="text-align: right;">Page 69</p> <p>1 programs are, the less likely that the patients who 2 are the most at risk are going to be able to qualify 3 without a support network -- either family, friends, 4 advocates or navigators. And in order to benefit from 5 new drugs, they must be available through insurance or 6 other programs. So, documenting improved patient 7 outcomes benefits patients, doctors and drug 8 developers. 9 Manageable and minimal side effects are 10 an important part of ensuring a good treatment 11 outcome. The limited drugs available to treat cocci 12 can have side effects that are as bad as the symptoms 13 of the disease. Patients want to resume our normal 14 lives. We want to go back to work or school and we 15 want to spend time with our family and friends again. 16 Many validated patient-reported outcome 17 surveys are available for evaluating the impact of 18 cocci. When evaluating which survey will be best for 19 your research project, there are some important 20 considerations. First, patients want to be heard and 21 many are eager to participate in our research. I've 22 had patients from Northern California ask about</p>

<p style="text-align: right;">Page 70</p> <p>1 driving all the way down to Bakersfield to take part 2 in our research. 3 We have a high participation rate among 4 our patients who have been asked to join our research 5 studies. There are some important factors of our 6 patient population that must be accounted for when 7 considering which surveys to use. First, the 8 population in endemic areas is heavily Hispanic and 9 any survey must be available in the dialects of 10 Spanish that are spoken in Mexico and Central America. 11 And in California, a variety of other languages 12 including Tagalog and Punjabi are helpful to have 13 available as well. 14 Low literacy rates among English and 15 Spanish speakers are prevalent in the areas endemic 16 for cocci. Materials that use simple language and 17 limit the number of questions are necessary to ensure 18 that surveys are accurate and completed. 19 What matters to research using 20 materials for health-related quality of life and what 21 matters to us as patients completing them are the 22 same: how a patient feels, how a patient functions</p>	<p style="text-align: right;">Page 72</p> <p>1 trials for drug candidates, both new drug candidates 2 but also candidates for repurposing to treat valley 3 fever. 4 So, I'm going to start by giving quite 5 a bit of credit to both the agency and NCATS from NIH 6 for the development of the CURE ID smartphone 7 application. If you have not downloaded it, I 8 strongly suggest that you do. It's a great 9 application that allows clinicians to report their 10 real-world experience with using both on-label and 11 off-label drugs to treat infectious diseases. And, of 12 course, valley fever, we posit that to definitely 13 benefit from the clinicians from the trenches treating 14 the patients, reporting their experience in a way that 15 is not intrusive, in a matter that is easy to comply 16 with, and without concerns for protected health 17 information being disclosed through the application. 18 The specific application that we 19 foresee for valley fever through the CURE ID program 20 and the CURE ID app is to be able to capture that real 21 world data of the experience of the clinicians 22 treating the patients with their results for the</p>
<p style="text-align: right;">Page 71</p> <p>1 and the survival of the patient. 2 Thank you for your time, and I'm happy 3 to share more information about my journey and 4 experience as well as the experience and stories from 5 some of our other patients that we have begun 6 collecting. Again, thank you for your time. 7 SUSAN HOOVER: Thank you, Rob. We now 8 have a period for formal public comments. There have 9 been two requests received to give comments. This is 10 a 15-minute interval, so these speakers will have 11 about seven minutes each. Our first speaker is Klaus 12 Romero of the Critical Path Institute. Dr. Romero is 13 the chief scientific officer at the Critical Path 14 Institute. 15 DR. KLAUS ROMERO: Thanks, everybody. 16 Just a quick sound check that you can hear me? 17 SUSAN HOOVER: Yes. 18 DR. KLAUS ROMERO: That's fine. So, 19 yeah, thanks for the opportunity. I'm actually very 20 honored to follow Rob in his presentation to talk 21 about real world data in how we can use and leverage 22 real world data to optimize the design of clinical</p>	<p style="text-align: right;">Page 73</p> <p>1 different drugs that are used and the different 2 experiences that are unique to each patient, as Rob 3 indicated his very informative presentation. 4 And the intention is to be able to 5 catalogue that real-world data to be able to then 6 generate actionable hypotheses and identify signals 7 that can be used to optimize the design of clinical 8 trials for valley fever drug candidates. 9 But in addition, things don't just stop 10 with leveraging the real world data to inform clinical 11 trial design -- the intention is to also be able to 12 have that information readily available for 13 researchers to also facilitate the advancement of the 14 real world evidence generation based on those real 15 world data that are captured through the application. 16 So, around the CURE ID app, the 17 Critical Path Institute has launched, funded by the 18 FDA, the CURE Drug Repurposing Collaboratory or CDRC. 19 And Marco Schito, who's on the phone with us today, 20 acts as the Executive Director for this effort. The 21 mission of the CURE ID -- of the CURE Drug Repurposing 22 Collaboratory revolving around the CURE ID app is to</p>

<p style="text-align: right;">Page 74</p> <p>1 essentially become that central global hub for real 2 world data to be integrated and to leverage the real 3 world data to generate real world evidence than can be 4 then leveraged to inform and optimize the design of 5 clinical trials to test different drug candidates 6 against a myriad of disease, as I'll explain in a 7 minute, but of course we definitely see -- and the 8 Critical Path Institute being based in Arizona, we 9 recognize the impact of valley fever, and we 10 definitely recognize the opportunities that are ahead 11 with the collaborator to impact drug development in 12 valley fever.</p> <p>13 So, this is a snapshot of how the 14 collaborator is structured. So, we have the advisory 15 committee made up of C-Path, FDA and NIH or NCATS 16 representative. And then we have a different set of 17 working groups that are focused on infectious diseases 18 on one hand and certain oncology indications on the 19 other hand. And you can see that we're running a 20 pilot project with the disease of the hour, COVID-19, 21 but we're very interested in setting up and 22 formalizing the working group for valley fever. And</p>	<p style="text-align: right;">Page 76</p> <p>1 participating in the collaboratory. And at a minimum, 2 give CURE ID a check because it's really worthwhile as 3 a resource for clinicians in the trenches. So, yeah, 4 with that, I'll stop. Thank you so much.</p> <p>5 SUSAN HOOVER: Thank you, Dr. Romero. 6 And our final public commenter is Dr. Gray Heppner. 7 Dr. Heppner is the Chief Medical Officer of Crozet 8 BioPharma, and I'm hoping he will correct my 9 pronunciation.</p> <p>10 DR. GRAY HEPPNER: Thank you. Can you 11 hear me?</p> <p>12 SUSAN HOOVER: Yes.</p> <p>13 DR. GRAY HEPPNER: Good. First of all, 14 thank you so much for allowing me to touch on the 15 related topic of vaccine development for 16 coccidioidomycosis. A vaccine is needed, it's 17 feasible and it's cost-effective -- but where is it? 18 There is a strong imperative for a stronger public- 19 private vaccine partnership to bring forth a much 20 needed public health measure.</p> <p>21 Who needs a vaccine? I think we've 22 heard today from the very moving patient testimony,</p>
<p style="text-align: right;">Page 75</p> <p>1 being in Tucson, of course, we're in the stages of 2 setting up the collaboration with the U of A, John 3 Galgiani and colleagues.</p> <p>4 And then we have the other working 5 groups that are going to be dealing with the data 6 analytics. That's more the world of the Quantitative 7 Medicine Program at C-Path. And then, of course, a 8 regulatory science workgroup that is going to interact 9 with the regulators to, again, organize the real-world 10 data into real world evidence that becomes actionable 11 to optimize a whole process for medical product 12 development against valley fever.</p> <p>13 And another important aspect that is 14 not captioned on the slide but an aspect that we 15 incorporate in every single one of our collaborative 16 efforts at C-Path is the patient representation. So, 17 Rob, we would love to follow up with you after today 18 to discuss options for collaboration.</p> <p>19 And so, with that, I'll stop and -- I 20 did it pretty much on time, so, yeah, that was that. 21 Thanks again for the opportunity and we look forward 22 to hearing from you if you are interested in</p>	<p style="text-align: right;">Page 77</p> <p>1 from epidemiology reports and from clinicians that a 2 vaccine is needed. This disease is devastating, it's 3 unavoidable and it's difficult to treat. And like so 4 many problems in life, prevention is worth more than a 5 cure.</p> <p>6 Who needs it? It's people who live 7 across the Americas, North America, Central America, 8 South America. It affects the most disadvantaged 9 people among us as well as people who don't think of 10 themselves as disadvantaged. But a vaccine is clearly 11 needed for these high-risk groups, older adults, very 12 young, military personnel on training maneuvers, 13 immunocompromised, working transplant patients, 14 certain ethnic groups -- African-Americans, prisoners 15 and people whose occupations do not allow them to 16 escape the exposure to this essentially unpreventable 17 exposure and disease.</p> <p>18 I think it's worth bearing in mind some 19 very simple observations about coccidioidomycosis. 20 First of all, a valley fever vaccine is feasible. And 21 why do we say that? Well, firstly, human infection is 22 protective against subsequent infection of disease,</p>

<p style="text-align: right;">Page 78</p> <p>1 demonstrating that almost all people's immune systems 2 are able to mount an effective immune response after 3 exposure. 4 A live attenuated spore-based vaccine 5 has been developed. We heard about this earlier as a 6 collaboration between Anivive, the University of 7 Arizona, and other parties. The vaccine has already 8 been proven safe and protective in mice and dogs 9 against the human pathogen, and it's encouraging that 10 a public-private venture is underway. 11 I would be remiss not to note the 12 importance of public sector support, particularly DMID 13 NIH support, which we heard about earlier, to 14 facilitate the important basic science, immunology, 15 proof of concept in preclinical models and toxicology. 16 It's my point of contention that the same vaccine is 17 likely to be safe and effective for humans that will 18 require substantial additional work. This is a 19 clinical grade manufacturing known as GMP, and careful 20 clinical development to demonstrate actual efficacy. 21 So, like so many infectious disease 22 problems that affect mankind, we know that vaccines</p>	<p style="text-align: right;">Page 80</p> <p>1 utilized are sadly lacking. 2 Incentives are needed for industry to 3 invest in a vaccine to protect people at risk of these 4 and other unpreventable diseases. People may ask why 5 does cocci lag behind? Well, it doesn't seem to 6 affect enough people to merit financial interest from 7 pharma. CEPI, the Coalition for Epidemic Preparedness 8 & Innovation, has addressed these gaps for diseases 9 which affect larger groups of people. But here, we 10 today are gathered to talk about why and what needs to 11 be done to solve the valley fever problem. It does 12 disproportionately affect poor and marginalized 13 populations. The potential direct market has not 14 catalyzed commercial vaccine efforts. 15 I'd like to mention and bring to your 16 awareness today the Priority Review Voucher. This 17 device, which is authorized by the FDA, would enable 18 vaccine developers to develop vaccines because it 19 would incentivize the development. It would provide a 20 pull mechanism to reduce risk for vaccine developers 21 who are on the margins or on the fences about 22 investing the initial effort to bring something</p>
<p style="text-align: right;">Page 79</p> <p>1 are feasible, they've often times been demonstrated in 2 preclinical models against human pathogens and yet 3 they don't exist. The late Adel Mahmoud at Princeton 4 as well as Stanley Plotkin and other advanced leaders 5 in vaccinology made the observation that there are 6 numerous infectious diseases that regularly claim 7 untold numbers of lives around the world; that there 8 are few vaccine candidates for combatting these 9 ailments. The reasons are not new. The 10 pharmaceutical industry may deem the markets not 11 sufficiently profitable to recover investments, and 12 government has not provided sufficient incentives. 13 So, what I'm referring to now is what 14 we in vaccine development called the valley of death 15 - the developmental valley of death, which is almost 16 as foreboding as the valley fever itself. Looking 17 from left to right, I think this is a well-circulated 18 diagram outlining the basic fundamentals of vaccine 19 development. It's important to both academics, and 20 NIH funds the basic research, but after this, the 21 translation into clinical development and eventual 22 life insurance so that the countermeasures can be</p>	<p style="text-align: right;">Page 81</p> <p>1 forward from proof of concept through GMP manufacture, 2 phase 1, phase 2, phase 3 and licensure. 3 Recently, a group of academics together 4 with support from certain Congressmen have asked the 5 FDA to approve a Priority Review Voucher to 6 incentivize the vaccine development for valley fever. 7 This was not accepted and an appeal is underway. But 8 I bring it to your attention today, and I thank you 9 for this time, as a needed incentive to help develop a 10 vaccine which would be of great benefit to people 11 across the Americas. Thank you again for this 12 opportunity to speak today. 13 SUSAN HOOVER: Thank you, Dr. Heppner. 14 There will be a lunch period now, and please be back 15 by 1:35 p.m., that's Eastern Time, for the start of 16 session two. 17 (Lunch Break) 18 COURT REPORTER: It's 1:35 p.m. 19 DR. JOHN GALGIANI: Great. Hi. This 20 is John Galgiani. I'm one of the session moderators 21 for Session 2. Janis Blair is the co-moderator. 22 Unfortunately, Janis is called away to cross-cover</p>

<p style="text-align: right;">Page 82</p> <p>1 another physician at her medical center and she 2 assures me that she'll get here just as soon as she 3 can, but that's the reason you've got me alone for a 4 little while here.</p> <p>5 I am going to introduce the first 6 speaker, who is Elizabeth O'Shaughnessy. Dr. 7 O'Shaughnessy is a clinical reviewer in the Division 8 of Anti-Infectives at the SEA. Dr. O'Shaughnessy? 9 DR. ELIZABETH O'SHAUGHNESSY: Thank 10 you, Dr. Galgiani. Good afternoon, everyone. During 11 the next 20 minutes I would like to cover regulatory 12 and clinical trial design considerations which are 13 applicable to the drug development for cocci. And 14 this will be a high-level talk, and there is some 15 overlap between this presentation and the FDA 16 presentation yesterday, so participants who are 17 attending both workshops may hear some of the same 18 information.</p> <p>19 So, by way of background, the FDA has 20 recently seen renewed interest in drug development for 21 cocci and, therefore, this is an opportune time to 22 discuss this topic and for us to better understand the</p>	<p style="text-align: right;">Page 84</p> <p>1 Foxmanogepix. And property available information on 2 these drugs is available in the reference slide.</p> <p>3 So, regulatory pathways for approval 4 include traditional approval, which is generally based 5 on a clinical endpoint measuring how a patient feels, 6 functions, or survives. An accelerated approval is 7 based on surrogate endpoint that is reasonably likely 8 to predict clinical benefits or on a clinical endpoint 9 that can be measured earlier than irreversible 10 morbidity or mortality.</p> <p>11 So, the limited population pathway or 12 LPAD is for drugs that are intended to treat a serious 13 or life-threatening infection in a limited population 14 of patients with unmet medical needs. Examples of 15 recent approvals in this LPAD pathway include 16 Pretomanid as part of a regimen for the treatment of 17 extensively drug-resistant tuberculosis or intolerant 18 or nonresponsive multidrug-resistant tuberculosis; and 19 then Arikayce for the treatment of pulmonary 20 nontuberculous microbacterial infection.</p> <p>21 Just to go into a little bit more 22 detail about accelerated approval -- accelerated</p>
<p style="text-align: right;">Page 83</p> <p>1 challenges involved. The general principles for 2 antifungal drug development are similar in many 3 aspects to those for antibacterial drug development, 4 however, there are particular challenges with 5 antifungal trials. For example, patient recruitment 6 and, of course, financial challenges. So, this talk 7 will include an overview of the regulatory approval 8 pathways, available incentives, the general content of 9 an NDA package, and clinical trial design 10 considerations.</p> <p>11 So, as you all know, there are two FDA- 12 approved drugs for the treatment of cocci, 13 Ketoconazole and Amphotericin B deoxycholate. And the 14 current standard of care includes Fluconazole, 15 itraconazole, or Amphotericin B in more disease. And 16 other treatment options include azoles such as 17 voriconazole or posaconazole.</p> <p>18 So, at this time, we have no approved 19 new drug application for cocci for decades but there 20 is hope. Examples of investigational drugs studied in 21 phase 1 human studies and in animal models of cocci, 22 include VT-1598, Nikkomycin Z, Olorofim, and</p>	<p style="text-align: right;">Page 85</p> <p>1 approval is appropriate for drugs and candidate to 2 treat serious condition and generally provides a 3 meaningful advantage over available therapies and 4 demonstrates an effect on a surrogate endpoint or an 5 intermediate clinical endpoint that is reasonably 6 likely to predict clinical benefit. It is important 7 to note that the trials meet the same statutory 8 standards for safety and effectiveness as traditional 9 approval.</p> <p>10 And this pathway has been primarily 11 used in settings where the disease course is long, and 12 an extended period of time would be required to 13 measure the intended clinical benefit of the drug. 14 So, it has less of a role in acute infectious 15 diseases. And for drugs granted accelerated approval, 16 post-market confirmatory trials have been required to 17 verify the anticipated clinical benefit.</p> <p>18 Now I'm going to switch to available 19 incentives. And many of you are familiar with the 20 Qualified Infectious Disease Product designation. 21 Drugs being developed for treatment of cocci may be 22 eligible for QIDP designation and it can be requested</p>

<p style="text-align: right;">Page 86</p> <p>1 at any time before submission of an NDA. QIDP 2 provides for an additional five years of marketing 3 exclusivity for certain drugs and for a priority 4 review for the first application for QIDP. And the 5 priority review timeline is six months, as compared to 6 ten months for standard review. And drugs that have 7 QIDP designation are also eligible for fast track 8 designation. And many of the drugs that currently 9 have QIDP also have fast track. 10 So, fast track designation can be 11 requested if the drug is intended, whether alone or in 12 combination, for the treatment of a serious or life- 13 threatening disease and it demonstrates the potential 14 to address unmet medical needs for such a disease or 15 condition. 16 And the information available to 17 support designation will depend on the stage of the 18 drug development. So, the supportive evidence could 19 include activity in a nonclinical model, a mechanistic 20 rationale, pharmacologic data, or available clinical 21 data. 22 So, just some key points on fast track</p>	<p style="text-align: right;">Page 88</p> <p>1 adequately controlled clinical trial is required with 2 supportive evidence from nonclinical and in vitro 3 studies are an indication. And for those with orphan 4 designation, the statutory standard first needs to be 5 met, which is effectiveness demonstrated in an 6 adequate and well-controlled investigation. 7 So, supportive evidence from 8 nonclinical studies include information on the 9 activity of the drug, antifungal drug in vitro and in 10 animal models of disease. And we just heard a very 11 informative talk on the various animal models of cocci 12 from Dr. Shubitz. Some considerations for the design 13 of animal model studies are listed below. For 14 example, information like the route of drug 15 administration, the timing of the initiation of 16 treatment and outcome measures such as survival and 17 changes in fungal burden and target orient. 18 As we know, PK-PD assessments in animal 19 models provide valuable information for design of 20 clinical trials. The division does not have a 21 preferred animal model of cocci to assess antifungal 22 activity or for PK-PD assessments. Considerations</p>
<p style="text-align: right;">Page 87</p> <p>1 designation -- it allows for frequent interactions 2 between the review team, including pre-IND meetings, 3 end-of-phase 1 meetings, end-of-phase 2 meetings, etc. 4 It also allows for submission and review of portions 5 of the application known as a rolling review. And 6 just to note that the designation may be rescinded if 7 it no longer meets the qualifying criteria. 8 Then, finally, we have the breakthrough 9 designation. For breakthrough therapy designation, 10 the clinical evidence must show that the drug may 11 demonstrate substantial improvement over available 12 therapy on one or more clinically significant 13 endpoints. There is intensive guidance from the FDA 14 on the drug development program beginning as early as 15 phase 1. It could be eligible for priority review if 16 supported by the clinical data at the time of the NDA 17 submission, and the drug receives all the benefits of 18 fast-track designation. 19 The remainder of the presentation will 20 focus on the content of a new NDA application data 21 package and on aspects of clinical trial design. So, 22 when seeking an indication for cocci, at least one</p>	<p style="text-align: right;">Page 89</p> <p>1 should be given to the target infection sites when 2 selecting an animal infection model. And PK-PD 3 assessments from an animal infection model have the 4 potential to aid in selecting a dosing regimen for 5 clinical trials, characterize and compare the drug's 6 activity from clinically relevant exposure at the 7 target infection site, and provide supportive evidence 8 for the drug's activity. 9 These are some high-level points on 10 clinical trial designs. For non-inferiority trial 11 designs, one must be able to provide a data-driven 12 justification for the non-inferiority margin. A drug 13 or regimen recognized as a current standard of care is 14 acceptable as an active comparator and recent trials 15 for invasive fungal disease have used the NI trial 16 design. 17 A superiority trial design could 18 include a placebo where it's feasible and ethical, an 19 active control or an external control for single-arm 20 studies, for example, with contemporaneous matched 21 controls. 22 Moving on to clinical endpoints. So</p>

<p style="text-align: right;">Page 90</p> <p>1 that we're all on the same page -- so, a clinical 2 endpoint directly measures a therapeutic effect of a 3 drug, an effect on how the patient feels, functions, 4 or survives. Clinical endpoints for cocci will depend 5 on the spectrum of clinical presentation or on 6 patterns of disease, localized versus disseminated 7 disease, for example, and characteristics of the 8 patient population.</p> <p>9 A cocci scoring system has been used in 10 published cocci trials. One could consider a patient 11 reported outcome measure, as mentioned in an earlier 12 talk. And if a biomarker of disease is proposed, for 13 example, a serological marker or cocci DNA, it should 14 be reasonably likely to predict clinical benefit.</p> <p>15 To define a PRO, a PRO is a measurement 16 based on a report that comes directly from the patient 17 about the status of the patient's health condition 18 without interpretation of the patient's response by a 19 clinician or anyone else. And PROs can be useful for 20 clinical outcome assessments for chronic infections. 21 And we look forward (inaudible) to the discussion and 22 appropriate endpoints for cocci trials. This is a</p>	<p style="text-align: right;">Page 92</p> <p>1 appropriate safeguards need to be included in clinical 2 trials. A safety database at the proposed dose and 3 duration is likely to be small in cocci trials; 4 therefore, additional safety data may be needed if 5 there is a significant safety signal. Additional 6 safety data may be requested through a post-market 7 study or enhanced pharmacovigilance post-approval.</p> <p>8 In summary, the presentation provided a 9 high-level review of some key considerations for drug 10 development for cocci, which include regulatory 11 pathways and incentives relevant to antifungal drug 12 development. And I just covered at a high level some 13 trial design aspects, endpoints, diagnostics and 14 safety considerations.</p> <p>15 As always, we encourage sponsors to 16 engage in early discussion and continue dialogue with 17 the Division of Anti-Infectives, and particularly when 18 planning novel approaches to clinical trial design. 19 There are some references, and just before I finish, 20 I'd like to acknowledge the contribution of Dr. Joe 21 Shane, clinical pharmacology, and Dr. Bala in 22 microbiology for their input, and thank you all for</p>
<p style="text-align: right;">Page 91</p> <p>1 very important aspect.</p> <p>2 What's the role of diagnostics? It's 3 important that the diagnostic test adequately detects 4 the disease of interest. This is especially important 5 in non-inferiority trials to ensure that the 6 population studied has the disease of interest. For 7 example, we've used the Galactomannan test in 8 invasive-aspergillosis trials for patient 9 identification and definition of patient populations.</p> <p>10 And, in general, diagnostic tests do 11 not have to be FDA-cleared or FDA-approved for use in 12 a clinical trial if being used for enrichment 13 purposes. If the diagnostic test is not FDA-cleared, 14 the information supporting the intended context of use 15 should be provided. And qualification of a diagnostic 16 as an endpoint is not a prerequisite for use in 17 clinical trials. And as you know, the CDER Biomarker 18 Qualification Program helps develop biomarkers as drug 19 development tools.</p> <p>20 So, the final word on safety -- 21 obviously, safety of study participants is paramount. 22 So, based on safety signals from nonclinical studies,</p>	<p style="text-align: right;">Page 93</p> <p>1 your attention. Thank you.</p> <p>2 DR. JOHN GALGIANI: Okay, thank you, 3 Dr. O'Shaughnessy, for the first presentation. I am 4 the second presenter today. I'm, as I said, John 5 Galgiani. I've been at the University of Arizona 6 faculty since 1978, and for pretty much all of that 7 time I've been interested in studying 8 coccidioidomycosis, and in 1996 founded the Valley 9 Fever Center for Excellence at the University of 10 Arizona.</p> <p>11 I'm also, in terms of disclosures, the 12 chairman of the board and a significant stockholder of 13 Valley Fever Solutions, which we'll touch on in terms 14 of the development of Nikkomycin Z, or the attempts to 15 develop Nikkomycin Z. It was the spinoff that we 16 created for that purpose to help move this drug along.</p> <p>17 So, the points that Dave Stevens and 18 others made this morning about the impact of valley 19 fever I think are very, very relevant. I'm not going 20 to try to reiterate any of those. But I would like to 21 make a comparison, which I find especially useful, 22 between the impact of valley fever compared to the</p>

<p style="text-align: right;">Page 94</p> <p>1 impact of polio in terms of rates per 100,000 people. 2 And you can see that the average number of reported 3 cases prior to their being a vaccine for polio was 4 about the same per 100,000 people for polio as it is 5 for coccidioides. And a parallel with polio occurred 6 at about the same frequency as disseminated disease. 7 There's a small problem or difference 8 between these two diseases in that polio is worldwide 9 and cocci is down to a very constrained part of the 10 world in those highly endemic regions. 11 So, like polio, I think of coccidioides 12 as a biohazard, albeit for a small endemic population 13 and the people who live there and the visitors. But 14 in the same way it is a biohazard for Americans and 15 for others in the Western Hemisphere. And where it's 16 endemic, I think we've seen the evidence that this 17 illness is anything but trivial. The impact -- 18 overall economic impact that I am starting to use is 19 about \$1.5 billion annually, and that's based in part 20 on Leslie Wilson's publication for costs of cocci to 21 California, and we replicated that model for Arizona, 22 and the two combined us just under \$1.5 billion.</p>	<p style="text-align: right;">Page 96</p> <p>1 1990 the experience of using Nikkomycin 2 therapeutically in mice. And in his study he had 3 eight mice that received no drug and eight mice who 4 received Nikkomycin. And the eight animals, very 5 similar to what Lisa Shubitz was showing -- they had 6 fungal growth with 2 times 10 to 6 (inaudible) units 7 per lung in the mice that got placebo, but in the 8 Nikkomycin, seven had sterile lungs and one had a 9 single colony grown. So, there was a very dramatic 10 difference with the therapeutic effect of Nikkomycin Z 11 that Richard found. 12 And if this were to hold up in human 13 trials, this would completely reverse the strategy. 14 And later, we'll be talking about therapeutic 15 strategies. But basically the strategy is to wait 16 until people develop complications and then 17 aggressively treat them. If we had a cure for this 18 disease, we would reverse that and try to diagnose as 19 early as possible all infections and cure it before 20 the complications developed. 21 So, the timeline as I said, this drug's 22 been around for quite a while. It was discovered by</p>
<p style="text-align: right;">Page 95</p> <p>1 Hers, Leslie's was for 2017, ours was 2019 for 2 reference years. And I think the public health 3 benefit clearly justifies the idea of trying to 4 develop better therapies and, in fact, vaccines. 5 However -- and this is the point that 6 I'll -- the lesson that I will try to emphasize in my 7 presentation -- the business model for developing 8 valley fever drugs and vaccines compete very poorly 9 against other investment opportunities. And that's 10 the theme that I'm going to try to develop here. 11 So, Nikkomycin Z has been around for a 12 long time. These cartoons show you the resemblance of 13 the drug, Nikkomycin Z, to the substrate for titin 14 synthase and, in fact, Nikkomycin Z is a competitive 15 inhibitor of titin synthases. 16 Here are a large list of fungi and 17 their MICs, and the one I want to point to is the one 18 on the top, which is -- sorry about that -- which 19 should be looped around coccidioides, which is by far 20 the lowest, .0625, compared to the other MICs in 21 vitro. 22 Rich Hector in the 1980s published in</p>	<p style="text-align: right;">Page 97</p> <p>1 Bayer in the 1970s. Rich Hector, the data that I 2 showed you was done in the 1980s. In the 1990s, 3 Shaman Pharmaceuticals initiated the development 4 program for Nikkomycin Z, but then went out of 5 business and that really slowed down progress, when 6 the company goes out of business. And it sat for five 7 years until the information and actually part of the 8 GMP-made drug that Shaman had done was transferred to 9 the University of Arizona, and we at the university 10 started to try to move this drug forward and we made 11 significant progress. 12 In 2006, we got orphan drug 13 designation, which, as you heard, gives you seven 14 years of exclusivity. We also initiated, because the 15 IND had been inactivated, we reactivated it and formed 16 Valley Fever Solutions to help us with development. 17 In 2014, we obtained a QIDP designation which adds an 18 additional five years to exclusivity, which for this 19 drug, being as old as it is, creates much of what we 20 depend on for protection for development. 21 And in 2015, we conducted a Phase 1, 22 two-week multidose study in 32 subjects and in 2019,</p>

<p style="text-align: right;">Page 98</p> <p>1 we had a pre-Phase 2 Type C meeting with the FDA. It 2 was to be face-to-face in Washington, but there was a 3 snowstorm, so from our hotel room we did it by 4 telephone, but it was a very productive meeting, as 5 those are. 6 And then we are continuing to improve 7 manufacturing processes and David Larwood has been 8 spearheading that, one of the speakers later in the 9 afternoon. So this is some data just to show you the 10 relationship, what we know about pharmacokinetics, 11 shown here is the human data from 250 q.12 up to 750 12 q.8 in oral dosing. This is a couple of data points 13 for mice on milligrams per kilogram on the X axis and 14 dotted throughout here are dog levels that Lisa 15 Shubitz did in a Phase 2 trial in therapeutics in 16 client-owned dogs. 17 And shown here as the ED 50 and ED 80, 18 are the effective AUCs in mice, and you can see that 19 clearly the absorption is sufficiently good that you 20 have good reason to think that if you went to a 21 clinical trial with any of these doses, it would be 22 done well and it would be certainly within the range</p>	<p style="text-align: right;">Page 100</p> <p>1 my comments, therapy is clearly an unmet need. I use 2 \$1.5 billion, but it's certainly, without quibbling, 3 that kind of a public health problem. The drug has a 4 novel mechanism of action. Its pharmacologic profile 5 is excellent and at this point, we see no evidence as 6 yet of any untoward reactions to the drug. 7 The experimental data in the mice 8 suggest it might be curative and the real issue is 9 that development is simply limited by finances. And I 10 think the take-home message is that the business 11 models for new Valley Fever therapies compete very 12 poorly against other investment opportunities. Future 13 paths forward likely will require a government 14 response to the public health need. I mean, this is a 15 public health problem and it is easy for me to see how 16 you might think that the -- it would be appropriate 17 for a federal support to help with this. 18 So where could that support come from? 19 Well, the FDA, we've heard some of the options they 20 have. I'm going to focus on the Tropical Medicine 21 Priority Review Voucher Program which just recently, 22 they decided at -- to determine that the request for</p>
<p style="text-align: right;">Page 99</p> <p>1 you might expect to see therapeutic results. 2 Here is, over the last 15 years, the 3 support we've gotten to do what I just summarized for 4 you, and you can see numerous funding items from the 5 NIH over the last 15 years. We've also had orphan 6 drug grant money from the FDA and we've had 7 philanthropic support from the JT Tai and Company 8 Foundation and also the Valley Fever of the Americas 9 Foundation, a foundation in Bakersfield. 10 Noticeably absent from this list is any 11 private investment, and that's kind of the point that 12 I'm going to try to make. This slide is not well 13 formatted for you, but shows you the Phase 1, which 14 goes up and Phase 2 that continues to go up and on the 15 right hand, in log scale, is cost of drug development 16 and as I think you know, even without this being 17 appropriately formatted, that the costs just continue 18 to go up. 19 Here we are at the beginning and this 20 timeframe going through Phase 2 and on to, hopefully, 21 approval at the FDA is where the real money is needed 22 for the final push. And so just to summarize, then,</p>	<p style="text-align: right;">Page 101</p> <p>1 coccidioidomycosis to be a part of this program should 2 be declined because it is -- has a potential 3 significant market for a vaccine. 4 I was quite surprised at that 5 determination and without going into that in any 6 detail here, I think we are hoping and others may be 7 hoping to put together a response to explain why we 8 think they should reconsider that. Also, we've seen 9 from the presentation from NIH now the SAnds is being 10 supported by NIH in the past and I think Neil Ampel 11 will likely touch on the Mycosis Study Group, maybe 12 Tony Catanzaro as well, about clinical trials we've 13 done in the past with NIH Contract Support. 14 That could certainly be resurrected, 15 but I think it would take a lot and I think we would 16 get a lot of benefit, in fact, from that kind of 17 support. And then finally, I think since I see this 18 as a biohazard that BARDA could easily be thought of 19 as appropriate to consider support for this. Even 20 though it's not a worldwide problem, it does impact 21 greatly Americans who live in or travel to these 22 endemic regions.</p>

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<p>1 So those are generally the comments I 2 had. I think that was my last slide and I thank you 3 very much for your attention and I see we're doing 4 very well on time and so I think with that, let me 5 introduce our third speaker, my good friend, Tony 6 Catanzaro.</p> <p>7 Dr. Catanzaro is a professor of 8 medicine at University of California San Diego who's 9 been working in the field of chronic pulmonary 10 infections including cocci, focusing on therapeutics 11 and diagnostics. Tony.</p> <p>12 DR. ANTONINO CATANZARO: Thank you very 13 much, John, and thank you to the organizers for 14 inviting me. Can you hear me okay? Is sound coming 15 through okay?</p> <p>16 DR. JOHN GALGIANI: Yes.</p> <p>17 DR. ANTONINO CATANZARO: Okay, good. 18 So yeah, thank you very much again for this invitation 19 and to provide a kind of -- almost a 50-year overview 20 of studies that I've participated in with a variety of 21 colleagues and we had a really good start, as you 22 point out, John, with the cocci study group when I was</p>	<p>1 of translating it from delayed type hypersensitivity, 2 cell mediated immunity and demonstrated a lot of T 3 cell dysfunction, both in lymphocyte transformation 4 and migration inhibition factor and other in vitro 5 studies of cell mediated immunity, and recognized the 6 similarly to the model that is shown here that Ward 7 Bullock presented for leprosy where delayed type 8 hypersensitivity was inversely coordinated with the 9 clinical disease, so when the disease was localized 10 with leprosy, there's a good delayed type 11 hypersensitivity response, went it disseminates and 12 these become more severe, delayed hypersensitivity is 13 markedly impaired.</p> <p>14 And that's very much the situation that 15 we saw with cocci and it's kind of made me think I was 16 aware of some studies that Sherwood Lawrence had done 17 in 1955 with transfer factor, which is a set of 18 proteins, soluble proteins derived from peripheral 19 blood that have the capacity to transfer delayed type 20 hypersensitivity as well as cell mediated immunity 21 from people who didn't have to people who had it -- to 22 people who had cell mediated immunity to people who</p>
<p>Page 103</p> <p>1 kind of lost at a California Thoracic Society meeting 2 with nowhere to go and Hans Einstein invited me to go 3 to the cocci study group meeting, which was an ongoing 4 organization at that time and over the years, has 5 developed quite nicely from a casual kind of sharing 6 of common interests into a very organized, scientific 7 organization for the presentation of data and for the 8 support of, at least emotional and scientific support, 9 for studies of various kinds.</p> <p>10 And I'm happy to say that the cocci 11 study group had a big part in my development and Neil 12 is going to go on and talk about future developments 13 as was pointed out.</p> <p>14 But one of the things that I learned 15 very early on is that the immune response to cocci was 16 very, very important and back in '72, it was 17 recognized that if you had -- if you didn't respond by 18 a skin test 1 to 10 coccidioidin, your chances of 19 having a very poor outcome and actually dying were 20 quite substantial.</p> <p>21 And based on that, I undertook a number 22 of studies of the cell mediated immune response, kind</p>	<p>Page 105</p> <p>1 didn't have it.</p> <p>2 And I wondered if this could help the 3 response in patients with coccidioidomycosis, and so 4 initiated with a whole bunch of colleagues, and I 5 think this is an important point to emphasize that 6 each study on coccidioidomycosis require a 7 collaborative group. There's no one center that 8 really sees enough patients to do a meaningful study 9 and you've got to bring people together.</p> <p>10 At that time, amphotericin was the drug 11 of choice, in fact, that only drug available and so 12 patients were having a tough time and so we decided to 13 continue the amphotericin but simply add transfer 14 factor. And we thought we had a really nice response 15 with 30 patients out of 49 having a favorable 16 response, but obviously without any controls, it was 17 hard to know what that really meant.</p> <p>18 And so we put together a plan to do a 19 double blind study, but NIH declined to fund it and so 20 we established the Cocci Cooperative Treatment Group, 21 a small group of unfunded trials, and we used the same 22 model where patients were treated with amphotericin</p>

<p style="text-align: right;">Page 106</p> <p>1 and transfer factor was added, but we did a double 2 blind. The transfer factor from coccoid in positive 3 donors, transfer factor from cocci negative donors, 4 and normal saline as a control. And unfortunately, we 5 were unable to see any different in the three groups, 6 whether by skin testing, by cell mediated immune 7 responses, or by clinical results. 8 So it was a complete failure. Luckily, 9 right around that time, there were a number of drugs 10 becoming available and we launched a series of studies 11 over the 40-some years which I'm going to review very, 12 very briefly today, starting with ketoconazole, and 13 studying patients with chronic pulmonary 14 coccidioidomycosis, and looking also at patients with 15 disseminated coccidioidomycosis, and I think that this 16 really started to bring home the fact that chronic 17 coccidioidomycosis is a very complex clinical 18 manifestation. 19 So in those days, the standard of 20 practice was not to treat people for cocci unless they 21 had symptoms or disease for six weeks or longer. That 22 meant we had chronic disease. But once you got to</p>	<p style="text-align: right;">Page 108</p> <p>1 So it really worked well in 2 infiltrative pulmonary disease and in soft tissue 3 disease, but we started to see weakness appear with 4 disseminated disease and with cavitary disease that 5 the responses were significantly less good when we 6 broadened the look from just the presence or absence 7 of cocci in the sputum to a broader mycosis study 8 group analysis. 9 We moved on to fluconazole, and 10 initially started with low doses of 50 to 100 11 milligrams in 14 patients and found that they were 12 definitely responsive, but relapses happened very, 13 very quickly and in very high numbers, so 50 to 100 14 milligrams is clearly not enough fluconazole. 15 This was backed up by in vitro studies 16 with serum concentrations of fluconazole at 50 and 100 17 milligram dosages and then with the good news that it 18 went on into CSF and so that opened up the possibility 19 of looking at meningeal disease and so we had a one- 20 armed study looking at 50 cases of cocci meningitis 21 treated with fluconazole and we had very nice 22 responses.</p>
<p style="text-align: right;">Page 107</p> <p>1 chronic disease, they went on for literally years and 2 just having a clinical response or, say, serologic 3 response was simply not enough. 4 You can see here that the responses 5 were not that good for pulmonary disease and were a 6 little better for disseminated disease, particularly 7 for synovitis, and for abscesses, but when you get to 8 osteo and abscesses, fistula, the persistence of 9 lesions was a really major problem with ketoconazole. 10 So at that point, we started to look 11 around and saw the mycosis study group had a scoring 12 system and we thought that would really be a good idea 13 to try to put that into effect and David Stevens 14 started to talk about that and we had a clinical score 15 based on clinical criteria, on radiographic criteria - 16 - obviously, this was focused more on pulmonary 17 disease -- and the serologic response. 18 And with that kind of a tool, we're 19 able to see for infiltrative disease we see right at 20 the beginning of disease, showing the scores across 21 that most patients had rather high scores, and then at 22 the end of treatment, they had low scores.</p>	<p style="text-align: right;">Page 109</p> <p>1 And I might say that there were no 2 withdrawals due to side effects, and at that time, we 3 thought that fluconazole had little or no side 4 effects, to this was pointed out by the patient 5 centered group, the side effects really were 6 significant, they just did some -- were overlooked in 7 those initial studies, and also were really relatively 8 low doses of 400 milligrams. 9 Moving on, we started a very nice study 10 with the mycosis study group involving chronic 11 pulmonary and non-meningeal disease and we had -- 12 where patients were started at 200 milligrams and non- 13 responders were moved up to 400 milligrams, and we see 14 here the slope down very nicely over a period of time 15 and then with the double blind study, which everybody 16 talked about, where we looked at fluconazole 400 17 milligrams versus itraconazole 200 milligrams in 18 patients in patients who had progressive, non- 19 pulmonary -- excuse me, nonmeningeal cocci. 20 We used the mycosis study group scoring 21 system at four, eight, and 12 months and we saw that 22 at eight months, 63 percent responded to fluconazole;</p>

<p style="text-align: right;">Page 110</p> <p>1 63 percent responded to itraconazole, so they were 2 pretty equivalent. For skeletal disease, there was 3 quite a difference with 57 percent responding to 4 fluconazole and 76 percent responding to itra, but he 5 P value wasn't really high enough and the big bad news 6 was that relapse rates were significant with 28 7 percent following fluconazole and 18 percent following 8 itraconazole.</p> <p>9 So this is the good, the bad, and the 10 ugly of fluconazole treatment that response rates were 11 pretty good, but relapse rates were rather significant 12 when drug was stopped.</p> <p>13 We went on to look at nonmeningeal 14 disease with posaconazole which was the first drug 15 that gave us any indication that there might be a 16 fungicidal drug. All the drugs up to this point are 17 fungistatic, but posaconazole had in vitro evidence to 18 suggest it was fungicidal, so we launched a study and 19 enrolled 20 patients.</p> <p>20 Unfortunately, the study was stopped at 21 173 days before the pharmaceutical company observed 22 toxicity in animals that they felt was simply</p>	<p style="text-align: right;">Page 112</p> <p>1 and the impact on the quality of life, both the 2 disease and the treatment are very significant and 3 were not at all recognized in these early studies but 4 has really come to bear fruit in recent analysis as 5 was pointed out very nicely by the patient centered 6 presentation we heard earlier.</p> <p>7 So we evaluate a series of increasingly 8 effective antifungals and maybe we're going to get to 9 fungicidal drugs, but starting with the fungistatic 10 drugs, there's often relapses following initial 11 treatment.</p> <p>12 So I want to acknowledge the pioneers 13 who participated in the cocci study group when I first 14 started up, and the continued activity of the cocci 15 study group, its evolution from sharing tales to a 16 really scientific group which is embarking on a new 17 frontier and I want to acknowledge the many, many 18 people who have shared my interest and enthusiasm and 19 point out that all the publications that I referred to 20 have been with collaborated -- hasn't been a single 21 pub that I've done with single authorship, not one. 22 And I want to thank the sponsors, both</p>
<p style="text-align: right;">Page 111</p> <p>1 unacceptable with the development of tumors in animals 2 and so they stopped the study, but we looked at the 3 results and we found that four had cultures at the 4 onset -- at the end of treatment, four had converted 5 to negative. Nine had a satisfactory response and 6 side effects were quite limited, so posaconazole 7 looked really nice in this very brief study of only 8 six months of treatment.</p> <p>9 So in summary, cocci is a very 10 complicated infection where simply eradicating the 11 fungus is just the beginning of the response to 12 treatment. There's a lot of tissue damage, 13 particularly in the lungs with chronic pulmonary 14 disease and that tissue damage opens the way to 15 secondary infections so that patients can get rid of 16 cocci and still be highly symptomatic and be quite 17 sick; and conversely, patients can be quite 18 asymptomatic, even with positive cultures, so it was 19 really complicate and requires an assessment to be 20 multidimensional.</p> <p>21 And again, that multidimensional aspect 22 we need to look at side effects in a very detailed way</p>	<p style="text-align: right;">Page 113</p> <p>1 NIH and CDC and pharmaceutical houses. A lot of the 2 studies that were presented were funded in part by NIH 3 and in part by pharmaceutical houses and I obviously 4 have to point out the patients who've been incredibly 5 tolerant in looking for new diseases, new treatments, 6 despite the fact that both the disease and the 7 treatment have great side effects. Thank you very 8 much for your attention.</p> <p>9 DR. JOHN GALGIANI: Tony, thank you 10 very much for your presentation. Our next speaker is 11 Dr. Royce Johnson. Dr. Johnson is an infectious 12 disease specialist with many years of experience in 13 multicentered, large and small clinical trials and 14 serves as medical director of Valley Fever Institute 15 at Kern Medical Center. Royce.</p> <p>16 DR. ROYCE JOHNSON: Thank you, John, 17 and thank you to the organizers. It's my pleasure to 18 be able to share some thoughts that come on the tail 19 of many of the things that have been said today. Wait 20 a minute. This is -- I'm having trouble advancing the 21 slide. It's not working. Let me try the computer. 22 No. Where's the arrow? Okay.</p>

<p style="text-align: right;">Page 114</p> <p>1 DR. JOHN GALGIANI: Royce --</p> <p>2 DR. ROYCE JOHNSON: So this is my only</p> <p>3 disclosure. I'm having trouble still with slide</p> <p>4 advance.</p> <p>5 DR. JOHN GALGIANI: Royce, below the</p> <p>6 slide there's a left and a right arrow on your --</p> <p>7 DR. ROYCE JOHNSON: I saw those and I</p> <p>8 was clicking on it, but it didn't want to move. Okay.</p> <p>9 So we skipped a slide. Can we go back? Yes. So I</p> <p>10 want to -- there's been several mentions about the MSG</p> <p>11 scoring system and the second part of my talk, I'm</p> <p>12 going to talk about this extensively, and I think it</p> <p>13 has been very important in the history of coccidioidal</p> <p>14 investigations. This was spearheaded by Bill</p> <p>15 Dismukes. I had the honor of knowing him and all four</p> <p>16 of the other authors, two of whom, I think -- one of</p> <p>17 whom, I'm sure, is here today with us electronically</p> <p>18 and that's Dave Stevens, but also Jack Bennett was one</p> <p>19 of the authors along with Dick Graybill and Stat Jack</p> <p>20 Remington. Those five, I knew them all. Some more,</p> <p>21 some less.</p> <p>22 This, my data comes on the tail of</p>	<p style="text-align: right;">Page 116</p> <p>1 from there.</p> <p>2 DR. ROYCE JOHNSON: Go back one. Let</p> <p>3 me just see where I was. Yeah, next slide, please.</p> <p>4 I'll just do that because I'm having trouble getting</p> <p>5 it to advance.</p> <p>6 coccidioidomycosis is a very</p> <p>7 complicated host-parasite relationship and Tony</p> <p>8 touched on that with his early transfer factor studies</p> <p>9 and studying the immunology of this disease and its</p> <p>10 immunogenetics is a key, I think, to going forward</p> <p>11 with disease understanding, but not our subject for</p> <p>12 today. Severe disease is failure of host defense, in</p> <p>13 my mind. Most of the time, I think that being more</p> <p>14 significant than differences in coccidioides</p> <p>15 pathogenesis or virulence. So the solution to this is</p> <p>16 newer and better antifungals, the main talk today,</p> <p>17 also immunomodulators and, of course, the holy grail</p> <p>18 being a vaccine that's effective. Next slide, please.</p> <p>19 The original MSG score was aimed at all</p> <p>20 fungal infections, not specific for cocci; although,</p> <p>21 there was specific reference to cocci and its</p> <p>22 chronicity and difficulty. It was generic. Since</p>
<p style="text-align: right;">Page 115</p> <p>1 David and John's and I actually -- the 150,000 number</p> <p>2 I have up there was from a David Stevens article. I</p> <p>3 do have some sources that think that the number of</p> <p>4 actual infections per year could be as high as</p> <p>5 350,000. David quoted 200,000. The fact of the</p> <p>6 matter is, I don't think we know, but I'm guessing</p> <p>7 that most of the estimates are actually on the low</p> <p>8 side.</p> <p>9 We all agreed based on C.E. Smith, that</p> <p>10 60 percent of the infections are asymptomatic, 40</p> <p>11 percent are symptomatic. About 10 percent are</p> <p>12 diagnosed and these are largely pulmonary and slightly</p> <p>13 different number than David; 1 percent disseminated</p> <p>14 which at the low end would be 1,500 infections a year.</p> <p>15 About half of these are meningitis and about half are</p> <p>16 not meningitis, meaning any other place in the human</p> <p>17 body can be infected with this fungus.</p> <p>18 There's some problem with advancing the</p> <p>19 slide.</p> <p>20 WOMAN 1: If you say next slide, we can</p> <p>21 advance for you on our end. Just let me know if this</p> <p>22 is the correct slide you should be on and we'll go</p>	<p style="text-align: right;">Page 117</p> <p>1 1980, obviously, we've learned a bit about this</p> <p>2 disease, perhaps not as much as I would have hoped,</p> <p>3 and the original MSG did not deal with the variety of</p> <p>4 nonmeningeal sites that occur. So I'll come back to</p> <p>5 this a bit later in the talk. Next slide, please.</p> <p>6 So we looked at all the studies where</p> <p>7 the MSG score had been used in cocci, many of which</p> <p>8 have been shown to us by Dr. Catanzaro. We also</p> <p>9 looked specifically at the search engines. We looked</p> <p>10 at the data from the FDA in their 2017 draft</p> <p>11 publication about multiple endpoints in clinical</p> <p>12 trials, which I'll come back to. In fact, first we're</p> <p>13 going to talk about clinical trials and the things we</p> <p>14 need to accomplish and second, we'll talk about</p> <p>15 revisions we've made to the MSG 2020 score that we</p> <p>16 think would make it a better tool for conducting</p> <p>17 trials. Next slide, please.</p> <p>18 So in getting a drug approval, you have</p> <p>19 to show two things. In the olden days, it was only</p> <p>20 number one, safety. But then came along the idea that</p> <p>21 you actually had to show drugs worked before you could</p> <p>22 sell them, and the concept is substantial efficacy.</p>

<p style="text-align: right;">Page 118</p> <p>1 Next slide, please.</p> <p>2 So I'm not going to spend any time on</p> <p>3 this, but the FDA, I think in particular wants to be</p> <p>4 sure that you conduct a trial that is not a chance</p> <p>5 win, meaning that the odds that the result occurred</p> <p>6 has to be something like less than 1 in 40. Then you</p> <p>7 have to have clinical importance, as in preventing</p> <p>8 death, but preventing mortality and other benefits are</p> <p>9 more difficult to prove but equally worthy. Next</p> <p>10 slide.</p> <p>11 I'm not going to go into this. Again,</p> <p>12 all of us are aware of this, that have ever done any</p> <p>13 kind of science, so the statistics of showing</p> <p>14 efficacy. Next slide, please.</p> <p>15 So endpoints have to be designated</p> <p>16 prospectively. Although I would -- of interest, I</p> <p>17 looked at remdesivir study recently and after the</p> <p>18 trial had started -- of course there was something of</p> <p>19 an urgency, wasn't it -- they actually changed some of</p> <p>20 their points during the course of the trial, but this</p> <p>21 is considered to be tacky unless you're dealing with</p> <p>22 an emergency. I'm not making any particular negative</p>	<p style="text-align: right;">Page 120</p> <p>1 of the population.</p> <p>2 The SAndS-PCC study is really the only</p> <p>3 major large study that is now ongoing and many of us</p> <p>4 are participating in that has tried to look at primary</p> <p>5 disease. Then also at the beginning of the trial, not</p> <p>6 later, you have to have an analytic program. Next</p> <p>7 slide, please.</p> <p>8 And that -- to show treatment effect,</p> <p>9 you have to have a point time estimate. Obviously,</p> <p>10 you have to have a P value, and to determine the</p> <p>11 significance, you have to have a confidence interval.</p> <p>12 Next slide.</p> <p>13 So cocci, as has been discussed at</p> <p>14 least somewhat, is a very complicated illness, in the</p> <p>15 sense that it's actually not an illness. It is a</p> <p>16 whole series of illnesses that are caused by the same</p> <p>17 fungus. It is going to be very difficult to not have</p> <p>18 multiple different outcomes in a cocci trial because</p> <p>19 of the nature of the disease.</p> <p>20 But the FDA in its wisdom has actually</p> <p>21 guidance in that document that I referenced earlier</p> <p>22 for having composite endpoints and you can have more</p>
<p style="text-align: right;">Page 119</p> <p>1 comment about that trial, but at any rate, the</p> <p>2 endpoints need to be of three types: primary, which</p> <p>3 should be single or few; secondary; and exploratory.</p> <p>4 Next slide, please.</p> <p>5 So we have to control prospectively,</p> <p>6 most of the time at least, endpoints. So if it's</p> <p>7 specific point in time and I think this could be a</p> <p>8 bone of contention in terms of cocci studies in</p> <p>9 particular. You'll notice that the MSG 2020 study or</p> <p>10 the MSG 20 study that was ITRA versus FLU that had a</p> <p>11 significant relapse rate was a one-year study. That's</p> <p>12 actually one of the longest studies that's been done</p> <p>13 in cocci.</p> <p>14 So the time to success in this fungus</p> <p>15 is longer and picking that time is, I think, critical</p> <p>16 to showing efficacy, albeit, if we had new fungicidal</p> <p>17 drugs, conceivably that time point could be moved</p> <p>18 back. Exploratory studies would have to be done, I</p> <p>19 think, to try and demonstrate that. You have to also</p> <p>20 define the population that you want to study and for</p> <p>21 the most part, our interest has been in studying</p> <p>22 people with disseminated disease, that very small part</p>	<p style="text-align: right;">Page 121</p> <p>1 than one clinical outcome, but all the outcomes need</p> <p>2 to be affected by the treatment and they need to be</p> <p>3 reasonably similar clinical importance. That last</p> <p>4 part is a bit of a stretch, but I think we can make</p> <p>5 those. Next slide, please.</p> <p>6 So multicomponent endpoints, within</p> <p>7 patient, two or more components. Observation of the</p> <p>8 specific components in that patient. You have to come</p> <p>9 up with a single overall rating determined by specific</p> <p>10 rules, hence the score system. The next words,</p> <p>11 ordered categorical or continuous numeric scales are</p> <p>12 deemed appropriate. I think this means that you can</p> <p>13 use ordinal or numeric data, either one. Next slide,</p> <p>14 please.</p> <p>15 So the MSG done in 1980 was about</p> <p>16 improving clinical relevance. Some parameters that</p> <p>17 are used in that score system are actually not easy to</p> <p>18 reproduce. I think many of us have had the experience</p> <p>19 of having our forehead temperature checked as we come</p> <p>20 in to work and found out that on a cold day, our</p> <p>21 temperature could be 93.5.</p> <p>22 So despite the fact that Santorius was</p>

<p style="text-align: right;">Page 122</p> <p>1 measuring clinical temperatures in 1592, and this 2 became a common measurement in the 19th century, we've 3 eliminated it from the score system. I know this is 4 anathema to infectious disease doctors who basically 5 view themselves as general practitioners for people 6 that have a fever, but we removed it.</p> <p>7 Headache, again there were scores in 8 the meningitis sections of the MSG score for severity 9 of headache. We have great trouble thinking that we 10 would get reproducible data from a variety of patients 11 in a variety of sites on monitors like that. So we 12 have made significant changes to the score system. 13 Next slide, please.</p> <p>14 So we looked for relevant clinical 15 manifestations of disease and variables that were 16 easily reproducible, especially across centers. Next 17 slide, please.</p> <p>18 So we retained pulmonary and 19 nonmeningeal as one score system, although I would 20 point out that, in fact, unlike the original MSG which 21 concentrated on chronic pulmonary disease, we didn't 22 include it. I think chronic pulmonary disease and</p>	<p style="text-align: right;">Page 124</p> <p>1 sections involve specific organ systems that are 2 involved in the disease. The first one is skin, which 3 is by and large the mildest disease. Next slide, 4 please.</p> <p>5 And then we went on to subcutaneous, 6 joint, and bone, all common site. Next slide.</p> <p>7 Intraabdominal, not a very common site, 8 but we do see it. Lymph node disease, as was 9 demonstrated in a slide of one of the previous 10 speakers. Then we left another slot for other sites 11 of dissemination, so that included the retina, which 12 we had a nice picture of earlier, or the epididymis -- 13 both begin with I -- E, I mean. Next slide, please.</p> <p>14 Then we retained the complement 15 fixation titers. We endeavored to shrink it. Some of 16 my colleagues balked at the -- how much we shrank it. 17 There is a question about this creating too much 18 weight on the complement fixation titer, but unsaid by 19 anybody at this meeting, the complement fixation titer 20 is both diagnostic and prognostic if it's performed in 21 the right laboratories, and for diagnosis and 22 prognosis in studies, there has to be tight control of</p>
<p style="text-align: right;">Page 123</p> <p>1 drug studies don't mix nicely, so we're really talking 2 about acute or really severe pulmonary disease and the 3 score system as reconceived by our group.</p> <p>4 Meningeal disease remains a separate 5 score system, although conceivably, they could be 6 combined if a study called for that. Severity is 7 based on clinical parameters, laboratory and 8 radiologic data. Next slide, please.</p> <p>9 So this is one of several slides that 10 I'm not going to go through, in fact, which is the MSG 11 2020 score system. NMD means nonmeningeal disease, so 12 it's divided into meningeal and nonmeningeal, so this 13 first set of slides is the nonmeningeal piece of the 14 score system as revised. So we have general things on 15 this slide -- next slide, please -- including the skin 16 test, you might notice.</p> <p>17 The pulmonary section was revised a lot 18 because we decided to look at severe pulmonary disease 19 rather than chronic pulmonary disease, so we've 20 divided it into people with modest respiratory 21 failure, the next line being people that have the 22 minimal requirement for ARDS. The next series of</p>	<p style="text-align: right;">Page 125</p> <p>1 where the laboratories are done, otherwise these are 2 of no benefit for diagnosis or prognosis, either one.</p> <p>3 We also gave scores for diagnostic 4 criteria, but we decreased the weight on these as 5 they're not easily available for all patients. Next 6 slide, please.</p> <p>7 So to -- we also changed the 8 categorization of scores in terms of percent 9 reduction. As was pointed out earlier in the original 10 score system for nonmeningeal disease, you had to have 11 a 50 percent score reduction to be called a success. 12 We adopted this terminology from the oncology 13 literature and so we have responders, partial 14 responders, non-responders, and progressors. This may 15 be contentious, but this is what we're thinking that 16 we might so. Next slide, please.</p> <p>17 This is the meningitis section. We 18 reordered the wording for level of consciousness to 19 modern Plum and Posner definitions. We also include a 20 section which we have liberally borrowed from our 21 cryptococcal colleagues on intracranial pressure, an 22 absolutely key thing to take care of in cocci</p>

<p style="text-align: right;">Page 126</p> <p>1 meningitis. We have some advances in neuroradiology 2 that I won't go into. Next slide, please. 3 We retained spinal fluid, as I call it, 4 the currency of cocci meningitis because you clearly 5 can have patients that feel wonderful on treatment but 6 have a spinal fluid that still looks terrible. 7 Actually, this has been a bone of contention between 8 John and myself for the last, how long, John? Twenty- 9 five years? Next slide, please. 10 So we retained the greater than 40 11 percent requirement to be called a success in 12 meningitis, but we did again add this oncology looking 13 partial responder, non-responder, and progressor idea 14 to the score system analysis. Next slide, please. 15 One second. I lost my picture. Rob of 16 our group gave a very nice talk about patient 17 suffering with this disease, which I noted when -- 18 every early in my career in cocci going back a lot of 19 years of people that suffered personal, financial, and 20 of course mortal results from the disease. 21 So at the suggestion of Jack Bennett, 22 we think that we should add to any analysis in any</p>	<p style="text-align: right;">Page 128</p> <p>1 controversy... if indeed such healthy discussion, 2 argument, and dialog ensues, then we will have 3 satisfactorily accomplished our goal." 4 And again, I want to thank my 5 collaborators at the Valley Fever Institute, Jack 6 Bennett for looking at some of our thoughts before 7 this talk, and John Rex, as well. And thank all of 8 you for your attention. 9 DR. JOHN GALGIANI: Thank you very much 10 Royce. That's very good and I'm delighted to say 11 we've done wonderfully on our time. We're now here 12 for a break and I think we'll just reconvene at the 13 time schedule which is 2:55, so we'll have a little 14 more than 15 minutes to get started. I think we 15 should stay at time so the people that were planning 16 to be on this agenda by the announced schedule will 17 find us there at the time we're supposed to be after 18 the break. So 2:55. 19 (Break) 20 DR. JOHN GALGIANI: John, are you with 21 us? 22 DR. JOHN REX: I am.</p>
<p style="text-align: right;">Page 127</p> <p>1 study we do an analysis of patients' perception of 2 their illness and the results of their treatment and 3 so the vehicles for that, the SF 12 version 2 is being 4 used along with the PROMIS and the SAnds-PCC, so we 5 have some familiarity with that. 6 Jack actually suggested the SF-36 which 7 some of my patients have objected to that when we've 8 tried it because of its length, and then in talking 9 with John Rex, the EQ-5D-5L he thinks is a beneficial 10 way to gauge outcome in trials. Perhaps on its own 11 merits only. I think it don't quite agree with him 12 yet, but who knows. Next slide, please. 13 So in conclusion, we've endeavored to 14 develop a more complete and objective system of 15 evaluations and parameters that are clinically 16 available and reproducible and hopefully could meet 17 FDA guidance in an appropriate endpoint -- composite 18 endpoint. Next slide, please. 19 And from Bill Dismukes and his co- 20 authors, two of whom I think are present, "We hope the 21 spirit of these remarks will spark lively discussions 22 as well as constructive criticism, challenge, and</p>	<p style="text-align: right;">Page 129</p> <p>1 DR. JOHN GALGIANI: The floor is yours. 2 DR. JOHN REX: Okay, I just managed to 3 -- come on, computer. Here we go. There's a button 4 on my keyboard that locks up my screen and I bumped 5 it. So anyway, so John Rex here from F2G and many 6 thanks to the organizers. It's actually been a very 7 interesting conversation. It's good to get the 8 community together. 9 There are five industry speakers. We 10 have loosely coordinated, but it's really mainly so 11 that we would each come up with somewhat different 12 topics. There'll be some repetition and -- but our 13 theme was pick something out of what we have learned 14 and try to tell that story. And so here's the story 15 from F2G's perspective. 16 So understand the point I want to make, 17 you need to know a little bit about the compound we 18 have in Phase 2. It's called olorofim. It's a novel 19 mechanism antifungal that inhibits pyrimidine 20 biosynthesis. Its broad activity against the 21 ascomycete mold fungi, so aspergillosis, Lomentospora, 22 Scedosporium, all those things, but also histo,</p>

<p style="text-align: right;">Page 130</p> <p>1 blastospora, cocci, all the endemics. 2 And it has a very potent activity. It 3 appears to be fungicidal. It does not, however, work 4 for candida, crypto or (inaudible) because the inside 5 target is completely different, just is never going to 6 work. 7 Dosed as a 30-milligram tablet, it has 8 FDA Breakthrough Therapy Designation based on its 9 preliminary clinical data and its now in the middle of 10 a Phase 2 open level study, patient with mold invasive 11 fungal disease where the patients have limited 12 treatment options. Now, the point that I want to make 13 is that because of some data I'm going to show you on 14 the next couple of slides, we got interested in the 15 question of how could you design a randomized trial in 16 cocci, and this led us to the theme with endpoints. 17 We've already had some discussion about 18 that today and I think we'll discuss it more during 19 the Q&A. The endpoints that I'm most familiar with 20 for antifungals are, they'll some out of the classic 21 invasive molds trials. So 42-day all-cause mortality 22 is a reasonable endpoint for acute pulmonary invasive</p>	<p style="text-align: right;">Page 132</p> <p>1 fungal disease, especially IA. But it -- this turns 2 out not to work very well for cocci and the theme I'm 3 going to bring up here is that we need something else 4 because symptoms improve way before radiology and 5 mycology and the idea of a PRO is definitely going to 6 come up. 7 So here's a little bit from our 8 dataset. IN this study, as of about 10 days ago, we 9 had enrolled seven patients with symptomatic cocci. 10 They fall into David Stevens' category earlier of 11 active, progressive disease: lung, brain, bones, 12 skin. They had all had significant prior therapy, 13 months, in some cases years, with existing agents but 14 they all, at the time they were enrolled, had active 15 disease. They had problems that were not being solved 16 by what they were receiving. At this point, they have 17 been on the study for -- add about 10 to these 18 numbers, but basically a few weeks to over a year. 19 All of them have noted clinical 20 improvement within one to four weeks of initiating 21 olorofim. Major improvements in activities of daily 22 living and functional mobility. However, their</p>
<p style="text-align: right;">Page 131</p> <p>1 aspergillosis. 2 It does get entangled with underlying 3 disease a little bit, because patients who get this 4 infection also are -- have underlying syndromes that 5 put them at risk for dying for other reasons, and it 6 doesn't work at all for infections that progress 7 inexorably but slowly and that's going to be the case 8 with cocci. 9 EORTC-MSG built over time to an overall 10 clinical response endpoint that was described in 2008 11 and it is built from clinical, radiological, and 12 mycological responses and overall success logically 13 requires improvement on all three of these sub- 14 elements; whereas failure is likewise obvious, but the 15 category of stable, sort of an in between state, is -- 16 exists and is categorized as a failure. 17 And you can be a failure, for example, 18 by feeling better, but your radiology hasn't yet 19 improved. Same radiology but you feel better. That 20 can lead you to being a stable failure. And you know, 21 like the 423-day all-cause mortality, this system 22 works okay for the relative acute pulmonary invasive</p>	<p style="text-align: right;">Page 133</p> <p>1 radiology and their mycology changes at a snail's pace 2 and a case is instructive. 3 So this is a patient that we presented 4 or tried to present at ECCMID this year. You can find 5 the abstract in the ECCMID abstract book. A 45-year- 6 old male with diabetes who had mild CN -- clearly 7 pulmonary and CNS disease. The CNS disease wasn't a 8 big deal. It was his lung disease that was really 9 problematic. Progressive dyspnea, weakness, fatigue, 10 fevers. 11 He even had needed supplemental oxygen. 12 He was staying home using a walker and really 13 suffering and he got a little bit of everything over 14 time. You can see this list of drugs. It was not 15 making him better. He kept coming back to the ER 16 because he couldn't breathe. 17 We enrolled him on the study in May of 18 last year. 19 DR. JOHN GALGIANI: John, are you still 20 there? I don't hear Dr. Rex. 21 DR. JOHN REX: I'm back. The call got 22 dropped. Sorry. Can you hear me?</p>

<p style="text-align: right;">Page 134</p> <p>1 DR. JOHN GALGIANI: Good, and John, 2 unless you have some other arrangement with the 3 others, you're going to need to wrap this up in the 4 next minute or so.</p> <p>5 DR. JOHN REX: Okay. Well, I am about 6 to be done. So this guy steadily improved but at day 7 85 he was -- clinically he was better, but he was, as 8 an overall response, he was a stable failure. I can 9 tell you he's gone on. He would actually now be an 10 EORTC partial response based on improvements of 11 radiology.</p> <p>12 If not EORTC-MSG, then what? I would 13 just say that we've explored the idea of EQ-5D-5L 14 which uses a point score of 1 to 5 across five 15 dimensions of how do I feel and you code it 16 numerically and we'll still need to say that he did 17 not fill this out prospectively. We weren't smart 18 enough at the time to have this in place. We have it 19 in place now, but qualitatively, what he did with his 20 improvement is similar to what we see in the other 21 patients, too.</p> <p>22 So in summary, we have a clinical</p>	<p style="text-align: right;">Page 136</p> <p>1 WOMAN 1: I'm sorry. Let's just take a 2 two-minute break. They should be loaded and --</p> <p>3 DR. ED GARVEY: I could do this without 4 the slides. I could do it very quickly. It's a very 5 simple presentation, if that helps.</p> <p>6 DR. JOHN GALGIANI: What say you, AV? 7 WOMAN 1: Are you there? 8 DR. ED GARVEY: Hello? 9 WOMAN 1: Yes, go ahead and please 10 proceed. I apologize.</p> <p>11 DR. ED GARVEY: No problem, no problem. 12 So thanks to the FDA for organizing this and for 13 inviting Mycovia. Quickly, who is Mycovia? Mycovia 14 is really the continuation of Viamet Pharmaceuticals 15 and we have focused on developing the next generation 16 fungal CYP51 inhibitors by rationally designing an 17 increase in potency and selectivity.</p> <p>18 By definition, maximizing the 19 therapeutic index to be able to achieve greater 20 clinical efficacy with little or no side effects. We 21 have two compounds that are in development, 1161 is 22 our lead compound that is now in three Phase 3 studies</p>
<p style="text-align: right;">Page 135</p> <p>1 response approach based on the EORTC-MSG but it's 2 actually too slow. The clinical improvement is -- 3 gets way out ahead of radiology and serology and that 4 actually leads to stable disease for a long, long time 5 that gets categorized as failure.</p> <p>6 Further, disseminated cocci is quite 7 diverse. It's -- there's no real one set of symptoms 8 that's going to match everybody, as was -- been 9 discussed, and so a suggestion from our date is that 10 something really simple like EQ-5D-5L and maybe the 11 NIH PROMIS score could be used is not clear cocci- 12 specific elements are going to be all that helpful 13 because of the varied disease syndromes. Thank you.</p> <p>14 DR. JOHN GALGIANI: Thank you, John. 15 Glad to have you with us. Our next speaker is Ed 16 Garvey. Dr. Garvey is a consultant for Mycovia 17 Pharmaceuticals. Ed. No, that's not Ed's 18 presentation. That's half an hour from now. Ed, do 19 you have any slides?</p> <p>20 DR. ED GARVEY: I do. I do, John.</p> <p>21 DR. JOHN GALGIANI: Okay. AV, we need 22 -- to have slides for Dr. Garvey?</p>	<p style="text-align: right;">Page 137</p> <p>1 to be finished this year.</p> <p>2 The subject of this talk will be 1598, 3 and the -- really, there's two messages I want to 4 give. One is our experience to date with developing 5 1598, and that is the fact that we've done it by and 6 large through external funding. So that's the message 7 I want to give and it's similar to what John gave 8 earlier that there are a number of different avenues 9 that you can explore and we've taken advantage of 10 these, a lot of them through NIAID and we've had 11 R21/R33 grant through NIAID. We've had numerous 12 contract services through NIAID and we also had a 13 large DOD grant that really covered a lot of our GLP 14 safety studies, so by and large, we were able to get 15 1598 through the IND with external funding.</p> <p>16 We hope to also do a lot of the 17 clinical development. As Erin mentioned earlier, 1598 18 is poised to start its SAD study through DMID. They 19 are actually performing -- conducting that study and 20 we've proactively looked at a number of opportunities 21 to do the MAD study and to do Phase 2 and 3, again, 22 through external funding. We've taken a large</p>

<p style="text-align: right;">Page 138</p> <p>1 advantage of all the incentives that are available 2 through the FDA and we've, of course, used external 3 KOLs in terms of shaping our clinical design. So 4 that's the path in terms of 1598. 5 The message I want to give as far as 6 the future, is that we are continuing to use external 7 funding to progress 1598 and as John mentioned in his 8 talk, you're almost forced to do that because of the 9 lack of support that is seen either through large 10 pharma in terms of partnering or in terms of funding 11 opportunities through other avenues. 12 So and the other part of the puzzle 13 that we're grappling with is not only funding but how 14 to actually do the Phase 3 study in cocci, because of 15 all the points that have been raised both yesterday 16 and also today in terms of endpoints and disease 17 definition and numbers of patients, et cetera, et 18 cetera. 19 So therefore, our current development 20 path for 1598 is to focus on crypto -- cryptococcal 21 meningitis. We feel like there are a number of 22 external funding agencies that could provide funding</p>	<p style="text-align: right;">Page 140</p> <p>1 like I just described. 2 So those are the key messages I want to 3 basically repeat that have been said over the last 4 couple days and I'll turn it back to John. 5 DR. JOHN GALGIANI: Thanks so much, Ed, 6 for your presentation. Our next speaker is David 7 Angulo. Dr. Angulo is chief medical officer at 8 Scynexis. Dr. Angulo, are you with us? 9 DR. DAVID ANGULO: Thank you. Thank 10 you very much, John, for the introduction and thank 11 you for the invitation to participate in this 12 workshop. So I see that aren't really my 13 presentation, which is -- should also be there, but 14 let me just briefly introduce you why we're interested 15 about -- why we have an interest about this topic. 16 We are developing ibrexafungerp. This 17 is an oral glucan synthase inhibitor. It's 18 structurally distinct from the other glucan synthase 19 inhibitors that are right now out there like the 20 echinocandins and as such, it has oral bioavailability 21 and it has activity as suspected for the glucan 22 synthase inhibitors for candida, aspergillus,</p>
<p style="text-align: right;">Page 139</p> <p>1 for those studies and the medical need for crypto is 2 so huge it's hard to ignore and in addition to that, 3 the importance of having very robust networks that 4 have been built by folks like Tom Harrison and Jeremy 5 Day make that a doable approach, we feel, and that in 6 parallel to that, we hope to possibly explore cocci by 7 a grant, possibly a U01 grant opportunity and to use a 8 design that has been talked quite a bit about in a 9 Phase 2 type POC study. 10 The only other thing I want to mention 11 is a couple thoughts that have -- were raised 12 yesterday to increase the enrollment numbers would one 13 consider expanding to all endemics, histo and blasto, 14 or would that complicate matters too much, and I think 15 the consensus yesterday was that it wouldn't, that the 16 increased enrollment would outweigh those 17 disadvantages. 18 And then the other idea is to really 19 focus on crypto as our additional robust clinical 20 trial design and approval in establishing a robust 21 safety database and then possibly is there an avenue 22 to get approval for cocci through a smaller study,</p>	<p style="text-align: right;">Page 141</p> <p>1 pneumocystis, and also for coccidioides and the other 2 endemic microbes as well. 3 Interesting, we have some very high 4 tissue distribution, so typically the concentrations 5 that we achieve in the tissues are very, very high -- 6 higher than they will normally see, let's say, with 7 the other glucan synthase inhibitors, and we are 8 conducting -- we have conducted a series and we are 9 conducting a series of different clinical trials in 10 different indications. We have completed our Phase 3 11 programming in vulvovaginal candidiasis. We are 12 ongoing with our studies in recurrent VVC, invasive 13 aspergillosis, and Candida auris infections. And for 14 the interest of this particular talk, we do have a new 15 study that is ongoing for refractory invasive fungal 16 disease. That is for a serious -- several infectious 17 diseases, fungal infectious disease that are included 18 in this program, in this protocol and 19 coccidioidomycosis is one of them. 20 So interestingly here, when looking at 21 the guidelines regarding what's right now recommended 22 for treatments, it's interesting to see that only one</p>

<p style="text-align: right;">Page 142</p> <p>1 of the products and actually -- well, not any longer 2 because amphotericin B deoxycholate is not recommended 3 -- that amphotericin B is the only one that actually 4 has something in their label that really8 speaks about 5 the indications of coccidioidomycosis. 6 Fluconazole, itraconazole, and all the 7 products that we had been hearing about often used for 8 this particular -- for this particular disease as the 9 standard of care, they simply don't have the 10 indication in the label and we wonder what may be the 11 reason for that. 12 And there is also interesting statement 13 in the idea saying 2016 guidelines for the treatment 14 of cocci that no clinical studies exist to guide the 15 optimal dose or duration of fluconazole or other 16 antifungal therapies for persons with primary 17 pulmonary coccidioidomycosis. 18 So that is definitely a gap there in 19 the research in this particular condition and let's 20 see what the -- why the gap may be. I think that we 21 have heard what are the challenges, but trying to 22 really focus on some of the areas that we consider may</p>	<p style="text-align: right;">Page 144</p> <p>1 nine sites in Arizona and California. If you look at 2 the sites, very reputable sites, however the study was 3 terminated because of lack of feasibility. So message 4 here is conducting clinical trials in cocci are not 5 that simple. It's complex. 6 Then treatment duration is long and 7 what that means, one of the implications of a long 8 treatment duration, at the bottom of the slide you see 9 an example here of a study that was fully presented 10 previously, the itraconazole versus fluconazole study, 11 to really the assessment of efficacy, the most 12 relevant assessment of efficacy occurred after eight 13 months and 12 months of therapy. So these are long 14 studies and what that requires is that you need to 15 have the numbers to do the study's long-term 16 toxicology. You need to have multiple efficacy 17 assessments and long-term treatment relations, which 18 really increases the drop-off rates and the overall 19 cost of the study and requires significant amount of 20 clinical trial supplies, just to get there. 21 And there are also market implications. 22 So let's say that about 12,000 to 15,000 people is</p>
<p style="text-align: right;">Page 143</p> <p>1 be responsible for this gap and what could be 2 opportunities to fill those. 3 So the studies in coccidioidomycosis 4 will be already -- are complex and the reality, they 5 don't happen quite often. And the number of cases 6 that we do have for this disease we need -- let's say 7 here, I'm just using CDC numbers, around 150,000 cases 8 a year. I can go, as we heard in previous 9 presentations, it could be substantially 10 underreported. 11 And they reported about 15,000 cases in 12 2018. So those are the cases that are likely to get 13 treated, the ones that get diagnosis and likely to get 14 treated. And so I think that the most recent study 15 that I saw in clinical trial that got treatment study 16 for cocci was this one that was attempted by NIAID. 17 It lasted from 2015 to 2018. They were trying to 18 enroll patients with pulmonary -- with pneumonia, 19 community acquired pneumonia and tried to see if early 20 treatment with fluconazole could have a benefit in 21 dose, particular endemic area. 22 The number of sites was quite good,</p>	<p style="text-align: right;">Page 145</p> <p>1 treated in a year. So what do we think that is going 2 to be the percentage of that market share for the new 3 agent? It probably depends on the difference in 4 attributes with these particular new agent may have, 5 it have -- I don't know, I have the percent cure rate 6 and certainly within three months of therapy probably 7 can take a very substantial amount of market share. 8 However, if you could rest on that, 9 it's very likely that currently available treatment 10 options that are genetic would likely to continue to 11 be used in a substantial proportion of these patients. 12 So really, the market share that you're going to get 13 out of these 12,000 cases a year is going to be a 14 smaller than the whole and then after you're able to 15 get approval, what is the market access that you're 16 going to get and what market access means. 17 It's actually the use of your product 18 because it is actually being reimbursed. So all these 19 institutions that are responsible for determining what 20 is get -- what gets reimbursed and what doesn't get 21 reimbursed, they really want you to show that either 22 you're superior to the current standard of care that</p>

<p style="text-align: right;">Page 146</p> <p>1 is very inexpensive, fluconazole generic, in order to 2 be able to allow for reimbursement of your drug, or 3 they will put your product on as second line therapy 4 that a patient needs to fail first the inexpensive 5 standard of care options before getting into the 6 treatment of this particular patient being approved. 7 So that even reduces ever more what is 8 your opportunities to really sell the product once it 9 is out in the market. 10 So I don't think that it's a mystery 11 here why there are so few runners in this race. So 12 clinical trials are complex, long, and not so easy to 13 enroll. There are not too many people. The cost and 14 time of development for traditional Phase 2 and Phase 15 3 randomized controlled trials versus the standard of 16 care is significant. The market opportunity is 17 limited and it's unlikely to grow significantly in the 18 upcoming years, let's say. 19 Difficult to predict what the market 20 access is going to be before having your Phase 3 data. 21 So how the -- one's to decide if this is going to be 22 reimbursed or not are going to -- how the decisions</p>	<p style="text-align: right;">Page 148</p> <p>1 commercial sustainability of a product once it is in 2 the market. Thank you. Thanks for the opportunity. 3 DR. JOHN GALGIANI: And thank you very 4 much. Our next speaker is Gareth Lewis. Dr. Lewis is 5 vice president of specialty brands at Mayne Pharma, 6 which includes responsibility for their antifungal 7 commercial on-market performance and development 8 pipeline. Dr. Lewis. Are you there, Dr. Lewis? 9 DR. GARETH LEWIS: Yes, thanks, John. 10 I was just coming off mute there. Yeah, thanks very 11 much. Appreciate the opportunity to participate and 12 speak, so I think -- if you could move to the next 13 slide. I'm going to actually have very similar 14 thoughts to those that David outlined a second ago, so 15 we're very much of the same mind in terms of the 16 challenges ahead. 17 Before that, let me just put into 18 perspective, Mayne's interest in participation in this 19 area. We have reformulated itraconazole oral products 20 which was -- obtained FDA approval about a year-and-a- 21 half ago, so yes, as with the other itraconazole 22 labels we're not indicated for cocci, but certainly</p>
<p style="text-align: right;">Page 147</p> <p>1 are going to be made before having the Phase 3 data is 2 very difficult to figure out. 3 The return on investment will likely 4 take a long time and so these are clear conclusions. 5 These are difficult to fund development programs via 6 traditional investors. I think that's the key reason 7 why there are few runners in this race. What helps -- 8 DR. JOHN GALGIANI: Dr. Angulo, we do 9 need to sort of wrap it up pretty quickly here. 10 DR. DAVID ANGULO: This is the last 11 slide. 12 DR. JOHN GALGIANI: Okay. 13 DR. DAVID ANGULO: Non-dilutive funding 14 to support Phase 2 and Phase 3 and then active 15 coccidioidomycosis clinical trial networks in order to 16 facilitate the (inaudible) start of these trials, 17 reevaluation of the endpoints which is happening in 18 please to hear in the past presentations. And a 19 streamlined regulatory path. The idea of yesterday of 20 really combining several conditions to really try to 21 get a study much more robustly and easy to enroll. 22 And for sure, we need to ensure</p>	<p style="text-align: right;">Page 149</p> <p>1 see an opportunity for its utility in this population. 2 So in recent times, we've been working 3 closely with the MSG ERC to conduct an endemic mycoses 4 clinical trial which is now close to completing 5 enrollment, so that's given us some direct experience 6 of enrolling and conducting a clinical study in this 7 patient population at the moment and it's a study 8 that's ongoing. It was targeted in a cohort for 9 approximately 20 proxy patients between California and 10 Arizona and other participating sites and this has 11 created some challenges, really, just because of the 12 analyses of infections and also year to year variation 13 in patient numbers. 14 So it is difficult to enroll and apart 15 from the number of infections which are -- we talked 16 about all day as being quite low, we often find that 17 patients will -- just will be triaged and assessed by 18 community physicians and won't always get referred on 19 to academic centers for evaluation and so yes, while 20 there might be patient numbers out there in the 21 community, those presenting and coming to trial sites 22 where many of the audience here today are leading</p>

<p style="text-align: right;">Page 150</p> <p>1 research at these hospitals, they don't always come 2 through and therefore by the time they get to these 3 hospitals, they're not always valuable for including 4 in the trial. 5 Our inclusion criteria were acute naïve 6 infections, so not disseminated to these or not 7 chronic, ongoing, challenging disease, so certainly if 8 you are seeking a trial where you are studying related 9 disease patients there's going to be even fewer of 10 those in circulation. 11 So yeah, certainly we are seeing that 12 it's very challenging to enroll and recruitment here 13 is -- can be years instead of months. A second point 14 is -- I'll be fairly brief on this. There's been a 15 lot of expert discussion on this already today. 16 Certainly the considerations of what constitutes 17 clinical benefit is very important. 18 Yes, there are hard clinical endpoints, 19 but then as the speakers before me just now have been 20 talking about, PROs, quality of life, symptom 21 management, disease burden, all these points are 22 really important to consider, especially as we then</p>	<p style="text-align: right;">Page 152</p> <p>1 So it's essential that we can generate 2 clinical data that really show an advantage and a 3 strong place and position for the new products that 4 are coming through and obtaining FDA approval so that 5 we can then have the strongest possible position to 6 take to the insurers to enable affordable patient 7 access. 8 So all in all, yeah, we see the same 9 challenges as my colleagues before me in terms of the 10 investment considerations. There is a small revenue 11 potential here, given the patient population and 12 market pricing. The cost barrier to develop is large 13 with long, complex trials and then there's the 14 significant execution risk with long trials, difficult 15 enrollment, the many other external factors that needs 16 to be taken to account before you can get to approval. 17 So all in all, yeah, to many 18 pharmaceutical companies that just really can't make 19 this investment consideration stack up to the 20 challenge because here we clearly see this as a 21 disease state that has many unmet medical needs and is 22 worthy of solid investment.</p>
<p style="text-align: right;">Page 151</p> <p>1 try to translate to what is the true socioeconomic 2 impact of disease and then as we have new therapies 3 that can benefit this disease, it's important that we 4 can demonstrate the improvement on such outcomes as we 5 can then get to a cost-benefit analysis of new drugs 6 as well as the clinical endpoints. 7 So really, that then takes us to the 8 commercial barriers which are very, very similar to, 9 as David ran through, something -- we agree entirely. 10 There are very few patient numbers. There are very 11 few patients are treated, and then as with our 12 existing low-cost alternative treatments, albeit off 13 label out there, the likelihood of product uptake is 14 fairly low. 15 So whilst this is an orphan disease 16 indication, the dynamics are very removed from some of 17 the rare oncology indications where drugs have a 18 significant premium or high value per patient. That's 19 not going to be the case here. So and thirdly, the 20 challenge of insurance coverage and patient access 21 restrictions as were mentioned a minute ago are very 22 relevant.</p>	<p style="text-align: right;">Page 153</p> <p>1 Those are my points. Thanks for your 2 attention and I'll pass the baton. 3 DR. JOHN GALGIANI: Thank you, Gareth, 4 very much. And our last speaker for this segment is 5 David Larwood. Mr. Larwood is CEO and president of 6 Valley Fever Solution. David, the floor is yours. 7 DAVID LARWOOD: Thank you, John. Thank 8 you everybody. Thank you to the NIH for this support 9 and to the FDA for sponsoring this excellent meeting. 10 Dr. Galgiani spoke earlier about the history of 11 nikkomycin Z and some of its attributes. A word about 12 -- first a couple of slides. This is the hyphae form 13 of the disease. This is a serial form of the disease 14 which many of you are familiar with. 15 I became a peripheral observer of the 16 cocci community as an infant when my father, Tom, did 17 a residency in Bakersfield under Chief Hans Einstein 18 after a bout of paralytic polio for my father and 19 myself, the family returned to Bakersfield as Dr. 20 Einstein was instrumentally involved in the 21 amphotericin trials for cocci, they became clinical 22 partners for decades.</p>

<p style="text-align: right;">Page 154</p> <p>1 Cocci, of course, expresses in these 2 horrible lesions so that's not -- oh these aren't 3 presenting well at all. Oh, heck. Those are nasty 4 picture of horrible diseases, so I'll just go on to 5 the next slide.</p> <p>6 The structure of the molecule resembles 7 a substrate per chitin synthesis as John mentioned in 8 his slides. The novel mechanism is fungicidal in many 9 instances, and in fact, it's so effective in impacting 10 chitin that it's used as a probe to study the 11 mechanisms of action, particularly in Canada. It's 12 been used a lot in Canada.</p> <p>13 It's demonstrated to be fungicidal in 14 mice and we have some interesting and recent results 15 we're anxious to publish fairly soon. I look forward 16 to telling you about them. So early publication by 17 Richard Hector which John mentioned, was the studies 18 in -- I don't see, do I have a pointer? Doesn't 19 matter. Sorry, studies in mice.</p> <p>20 So pulmonary infection, relatively low 21 dose gave a very high level of protection. In 22 meningococcal, meningocerebral version of the</p>	<p style="text-align: right;">Page 156</p> <p>1 screen's doing funny things to me. Anyway, so -- 2 sorry. The protective element of the azoles wears off 3 as soon as therapy stops; whereas in cocci is 4 persistent, so it's been judged to be fungistatic for 5 quite some time. Hopefully, the pointer goes away. 6 We'll make that go away. Okay.</p> <p>7 Talking about this slide, just -- I'll 8 touch more of my background. In my medicinal 9 chemistry PhD program at UCSF, I co-invented my second 10 commercial drug pegylated liposomes. About a year 11 later, members of our small group invented the first 12 amphotericin B liposomes. Continuing with the story, 13 trial strategy.</p> <p>14 This has been discussed really a lot. 15 I don't have a lot to add. All the considerations 16 that people have talked about are very important for 17 it to be working in these things. One of the 18 important characteristics for any drug that's being 19 developed is supply limitations. Can you manufacture 20 the quantities that you're going to need? There are 21 many points where people can trip up. 22 In preparing for an article I did</p>
<p style="text-align: right;">Page 155</p> <p>1 challenge 50 milligrams per kilogram gave a moderate 2 protection, but not really enough. Subsequent studies 3 have been very interesting. That'll be the subject of 4 a couple upcoming publications which we're excited to 5 share.</p> <p>6 Looking at -- Dr. Shubitz earlier 7 mentioned a couple of studies in natural (inaudible) 8 in dogs. This is one of them. The results were very 9 promising and although the population was very small, 10 a third of population reached near resolution in just 11 a two-month study. Dr. Johnson mentioned that it would 12 be interesting if a drug was fungicidal -- I'm sorry, 13 I skipped over that.</p> <p>14 One of the aspects of nikkomycin that's 15 been recognized for a long time, in the meningococcal 16 study, I don't have a good pointer here. Can I make 17 the pointer work? I can make the pointer work. So in 18 the azole treatment, it's protected during therapy and 19 then falls off sharply after therapy. That is 20 consistent with many, many observations and -- what's 21 it doing now? Okay.</p> <p>22 Sorry. The slide's doing -- my</p>	<p style="text-align: right;">Page 157</p> <p>1 recent -- looked at recent reviews and I thought this 2 chart from Rauseo and there was another interesting 3 one from (inaudible) at Davis that listed a chart of 4 drugs in development against a variety of fungi and 5 you'll see nikkomycin is listed in the column. They 6 didn't pick up the fact that in Canada, there's been a 7 lot of work done in Canada, but that's okay.</p> <p>8 You'll see the VT applied the VT series 9 and the olorofim series. Others that have been 10 discussed are also in this chart, but the point here 11 is that if you're looking for a rare disease like the 12 endemic fungi, only what, roughly half of these 13 candidates even are expected to touch the endemic 14 fungi, so this just illustrates that it's difficult 15 to do development in this area and that's going to be 16 hard for people who are -- the business evaluation.</p> <p>17 Several of the components that we look 18 at, nikkomycin is active against chitin which is very 19 involved with cell walls. So depending on what 20 organism you're looking at, the cell wall structures 21 could be quite different, and that has some relation 22 to which drugs are effective against which fungi and</p>

<p style="text-align: right;">Page 158</p> <p>1 why they're not effective against all of them.</p> <p>2 This illustrated how chitin is one of</p> <p>3 the core layers protecting the membrane and interfaced</p> <p>4 as it's tightly interlinked with the various beta</p> <p>5 glucans, so some of the most effective therapies.</p> <p>6 Nikkomycin is very effective as a monotherapy against</p> <p>7 endemic fungi, but it's effective against other fungi</p> <p>8 including aspergillosis when mixed with the anti --</p> <p>9 with the chitin in the beta glucan inhibitors, the</p> <p>10 echinocandins.</p> <p>11 You see quite a number of organ -- of</p> <p>12 drugs here being used to impact the cell wall</p> <p>13 structure. So this is considerations. I live for</p> <p>14 silicon -- I spent a decade as a VP at two startups in</p> <p>15 Silicon Valley including five years there as general</p> <p>16 counsel of a public company, buying and selling</p> <p>17 companies which informs my discussion a bit later.</p> <p>18 I became a full-fledged member of the</p> <p>19 cocci community in 2007 when I joined John at Valley</p> <p>20 Fever Solutions. For good measure, I finished a</p> <p>21 double MBA in 2009. Dr. Galgiani has submitted the</p> <p>22 business models for cocci drugs compete poorly in the</p>	<p style="text-align: right;">Page 160</p> <p>1 These are all plus factors for the business</p> <p>2 considerations.</p> <p>3 We talked about development costs.</p> <p>4 This chart was interesting. When I looked at it</p> <p>5 originally, I noticed that the anti-infectives list</p> <p>6 for Phase 3 trials is running about \$25 million.</p> <p>7 Yesterday, we heard stories where they could easily</p> <p>8 cost \$300 million or certainly well over \$100 million.</p> <p>9 So the --</p> <p>10 DR. JOHN GALGIANI: David --</p> <p>11 DAVID LARWOOD: -- average --</p> <p>12 DR. JOHN GALGIANI: You're going to</p> <p>13 need to sort of wrap it up in the next minute or so.</p> <p>14 DAVID LARWOOD: Okay. Well, that would</p> <p>15 be good. So, with averages and such, the trials are</p> <p>16 expensive. This also can impact the drug business</p> <p>17 prices. So looking at a decision tree, the invest --</p> <p>18 the money invested now is uncertain until you get all</p> <p>19 the way through this thing, so I just extracted this</p> <p>20 from a bio -- no, this was from ERC -- I think I got</p> <p>21 this from the NIH, the pages. The point is that if</p> <p>22 you get to success, it's wonderful but if you fall</p>
<p style="text-align: right;">Page 159</p> <p>1 business world. We've talked much of the challenges</p> <p>2 of trials, choosing endpoints and much more. For many</p> <p>3 investors, even the life sciences, there are</p> <p>4 alternative investments that simply seem more</p> <p>5 attractive. Our last two speakers, Dr. Lewis and Dr.</p> <p>6 Angulo point out the commercial difficulties and Dr.</p> <p>7 Rex is very well aware of the challenges of bring any</p> <p>8 drug forward.</p> <p>9 So the team. Who's involved in this</p> <p>10 thing? The technology. What's the answer, the</p> <p>11 solution, the target? Who interesting is the market?</p> <p>12 You could have a fabulous drug for a fabulous</p> <p>13 associated disease, that just isn't -- that isn't</p> <p>14 going to sell much product and competition by others</p> <p>15 and the time to when you can get there are important</p> <p>16 considerations.</p> <p>17 Fortunately for us in this space, the</p> <p>18 anti-infectives tend to do fairly well in trials, go</p> <p>19 from Phase 1 to Phase 2 to Phase 3 and through the NDA</p> <p>20 we scored generally high in the success rate, so</p> <p>21 that's helpful. Rare diseases tend to do a little</p> <p>22 better than average drugs, so that's also helpful.</p>	<p style="text-align: right;">Page 161</p> <p>1 even a little bit short of success, it's very costly.</p> <p>2 So that's another risk factor that business people are</p> <p>3 going to look carefully at.</p> <p>4 Projections show that the systemic</p> <p>5 antifungals that are used for Valley Fever about two-</p> <p>6 thirds, about \$1.8 billion of sales. If you look at</p> <p>7 specific drugs, it's interesting to note, these are</p> <p>8 just projections that I took from a model about a year</p> <p>9 ago so they were projected at the time. One thing you</p> <p>10 notice here is there are very long tails. Ampicillin</p> <p>11 is being reformulated. It's still selling at</p> <p>12 significant numbers. Fluconazole, which is decades</p> <p>13 old, is still selling and making money, so this is</p> <p>14 another factor in the business considerations. And I</p> <p>15 thank you for your time.</p> <p>16 DR. JOHN GALGIANI: David, thank you so</p> <p>17 much and you all have been really responsive to being</p> <p>18 in this tight timeframe. We have Janis Blair, my co-</p> <p>19 moderator with us, right, Janis? Are you with us?</p> <p>20 DR. JANIS BLAIR: Yes. Can you hear</p> <p>21 me?</p> <p>22 DR. JOHN GALGIANI: Why don't you take</p>

<p style="text-align: right;">Page 162</p> <p>1 over?</p> <p>2 DR. JANIS BLAIR: Okay. So the last</p> <p>3 speaker of this session will be Dr. Neil Ampel. Dr.</p> <p>4 Ampel is professor emeritus of medicine at the</p> <p>5 University of Arizona College of Medicine and my</p> <p>6 colleague as a supplemental consultant at Mayo Clinic</p> <p>7 in Arizona.</p> <p>8 DR. NEIL AMPEL: Can you all hear me,</p> <p>9 first of all? And this isn't my --</p> <p>10 DR. JOHN GALGIANI: Yes, Neil.</p> <p>11 DR. NEIL AMPEL: -- slide. Yeah, so I</p> <p>12 have to get my slides up, Janis and John. Have to go</p> <p>13 to the beginning. We'll wait on that. This is</p> <p>14 somewhere, not in the beginning at all. See if we can</p> <p>15 go -- there we go. I'll get -- okay.</p> <p>16 So I want to thank the organizers for</p> <p>17 asking me to talk. This is, I think, based on a</p> <p>18 discussion we had in the pre-meeting about how to move</p> <p>19 treatment studies for coccidioidomycosis further and</p> <p>20 so what I thought I'd do is talk -- use the past, tell</p> <p>21 us where we are, and make a suggestion for the future.</p> <p>22 So what was the past? Well, the past</p>	<p style="text-align: right;">Page 164</p> <p>1 other major members: David Stevens, Tony Catanzaro,</p> <p>2 Royce Johnson -- who are all on this call -- Dick</p> <p>3 Graybill is not.</p> <p>4 And the way it worked was there was</p> <p>5 industry funding that came into the particular study,</p> <p>6 but MSG provided administrative design and statistical</p> <p>7 support and I want to give a little shoutout to</p> <p>8 Gretchen Cloud because this was one of the ways MSG</p> <p>9 was so important. Gretchen was a statistician at UAB</p> <p>10 Cancer Center and she was just primary to both design</p> <p>11 of studies, implementation of studies, analysis of</p> <p>12 studies.</p> <p>13 Without her, many of these studies</p> <p>14 would not have worked, so that's what MSG added to the</p> <p>15 coccidioidomycosis subgroup, and I think it was</p> <p>16 critical.</p> <p>17 And this is just a short list of</p> <p>18 publications. These were ones that actually have</p> <p>19 NIAID Mycoses Study Group in the title. There are</p> <p>20 more. I think I left some David Stevens papers out,</p> <p>21 but if you just look at this short group, what you'll</p> <p>22 see is the iconic papers of antifungal therapy for</p>
<p style="text-align: right;">Page 163</p> <p>1 modern age of therapeutics was the Mycoses Study</p> <p>2 Group. This was started in 1978 as a contract through</p> <p>3 NIAID. It was awarded to the University of Alabama at</p> <p>4 Birmingham under William Dismukes as it's PI and its</p> <p>5 goal was to perform multicenter collaborative clinical</p> <p>6 trials for the prevention and treatment of invasive</p> <p>7 fungal infections.</p> <p>8 In 2005, the contract was terminated</p> <p>9 and that was effective in April 2007. And I think</p> <p>10 it's worth paying at least a little homage to Bill</p> <p>11 Dismukes who was a mentor to many of us on this call</p> <p>12 and the purpose here is not just to pay that homage,</p> <p>13 but to realize he was the brain child of the MSG and</p> <p>14 it was extremely productive in the years that it was</p> <p>15 funded.</p> <p>16 And this is the structure. I've lost</p> <p>17 some of the brackets here, but it'll still make sense.</p> <p>18 So the way this worked was NIAID funded MSG at</p> <p>19 University of Alabama Birmingham to design and</p> <p>20 implement studies on fungal diseases and as part of</p> <p>21 that was the coccidioidomycosis subgroup, of which</p> <p>22 John Galgiani was the subgroup leader and you see the</p>	<p style="text-align: right;">Page 165</p> <p>1 coccidioidomycosis, including treatment of meningitis</p> <p>2 with fluconazole and including the only comparative</p> <p>3 trial of two antifungals for cocci, which I'll go over</p> <p>4 in a bit.</p> <p>5 So that was the past. Where are we</p> <p>6 now? Well, as I said, since 2007, and actually well</p> <p>7 before that, there have been no controlled trials for</p> <p>8 coccidioidomycosis and the only comparative placebo</p> <p>9 controlled trial ever done was published in 2000 and</p> <p>10 that was the one that John was the lead author</p> <p>11 comparing itraconazole to fluconazole. We've had no</p> <p>12 other controlled trials.</p> <p>13 Since that time, we have case reports</p> <p>14 and case series and there's a huge problem with that.</p> <p>15 Case series are, by definition, inherently biased and</p> <p>16 I certainly published them and I'm very aware of those</p> <p>17 biases and we have to work around them because that's</p> <p>18 the only trials we have right now. But they're</p> <p>19 extremely problematic.</p> <p>20 First of all, they result in reduced</p> <p>21 strength of recommendations and we see that in the</p> <p>22 current guidelines where many things are not based on</p>

<p style="text-align: right;">Page 166</p> <p>1 randomized controlled trials. They are, in fact, 2 based on expert opinion which is problematic. For 3 example, I worked with John for 25 years. I now work 4 with Janis. We are all considered experts. We all 5 each treat coccidioidomycosis a little bit 6 differently.</p> <p>7 So if you ask John or Janis and me, you 8 might get a very different answer about how to manage 9 a case, because it's based on our experience. A 10 better example that I use because I don't want to use 11 anything topical, I used some many years ago in HIV, 12 the use of corticosteroids for pneumocystis. Prior to 13 randomized controlled trials, there were many case 14 reports. Some said, don't use steroids in 15 pneumocystosis. Others said, use it. Other said, use 16 it before. Others said, use it after.</p> <p>17 When we had two randomized placebo- 18 controlled trials funded by NIAID that showed that 19 starting corticosteroids at the time of antimicrobial 20 therapy for pneumocystis, led to marked reduction in 21 mortality, it was practice changing. It changed 22 practice, literally, the day those two papers came out</p>	<p style="text-align: right;">Page 168</p> <p>1 specific studies, and that's the place we've been in 2 now for the last 15 to 20 years.</p> <p>3 We've already said the cocci market is 4 small. So it's not an attractive target to develop 5 new antifungals and we really need something beyond 6 industry support alone to do good clinical trials.</p> <p>7 So what is the future? Well, first of 8 all, what are some of the present unanswered 9 questions? We've heard a couple of times about the 10 SAnds study, which I call the formerly known as FLEET 11 which is an attempt to understand how we manage 12 primary pulmonary disease and this is one of the 13 problems. There are two papers, one I authored with 14 John, another that Janis did, which suggest that 15 patients who don't get treated may do as well as 16 patients who do get treated and that treatment may not 17 prevent dissemination.</p> <p>18 But again, those were case control 19 studies and so they are inherently biased and so there 20 have been these attempts which we've heard today to 21 try to do a better study. That's still an open 22 question because this FLEET SAnds study was not well</p>
<p style="text-align: right;">Page 167</p> <p>1 in the New England Journal, so that's the strength of 2 doing controlled trials and not depending on case 3 series, which we are now.</p> <p>4 Now, you've heard over and over, over 5 the last few hours, why the present model that relies 6 on industry support is not adequate for therapeutic 7 trials in coccidioidomycosis. We've already heard 8 pharmaceutical companies currently operate under a 9 much stricter profit margin than they ever have in the 10 past. Cost of developing new drugs is prohibitive and 11 there must be a large market to support new drug 12 development.</p> <p>13 We've heard this all before. This is 14 just my take. You've heard others. I just looked at 15 invasive molds. There are about 180,000 16 hospitalizations for invasive molds over a 10-year 17 period. For cocci, it's about a fifth of that. so at 18 least five times lower. Moreover, the market for 19 preventive therapy for invasive mold disease is huge, 20 but it's small for cocci. So what does this lead to? 21 Developing antifungals for the larger market and then 22 using them because they're available for cocci without</p>	<p style="text-align: right;">Page 169</p> <p>1 designed.</p> <p>2 What's the best antifungal for 3 nonmeningeal disease? As you saw, we keep using 4 fluconazole. Is that really the best drug or are 5 there others? What about pulmonary versus 6 disseminated? Even more important, management of 7 coccidioidal meningitis. What's the best antifungal 8 there? Again, we are often trapped to use fluconazole 9 and only use other agents after the patients fail. So 10 what's the best triazole? What about newer 11 antifungals like olorofim?</p> <p>12 What are -- what should we do there? 13 And therapy ever be stopped? What's the role in 14 intrathecal amphotericin B, another area where experts 15 disagree? And what's the role of intravenous 16 amphotericin B? So there are many questions. And 17 finally, we need more answers on the patients on 18 biologics and transplants.</p> <p>19 So what should be the future? Well, 20 many people have proposed, well what about the 21 Coccidioidomycosis Study Group? And some people 22 suggested -- I'm now the current president -- well,</p>

<p style="text-align: right;">Page 170</p> <p>1 you guys do studies, and so I want to explore that for 2 a bit. This is the definition of the cocci study 3 group that is on the University of Arizona Valley 4 Fever Center for Excellence website, and I think it's 5 very accurate except for one area and that's research 6 studies.</p> <p>7 So I'll come back to that. But I want 8 to take a more granular view of the cocci study group 9 because I think a lot of people who aren't involved 10 with it think it's a little more than it may be.</p> <p>11 First of all, it's a non-affiliated organization whose 12 primary goal is to host an annual meeting dedicated to 13 presenting new information and research on cocci. And 14 it does that very well.</p> <p>15 I would say in the last decade the 16 presentations there rival any at any national or 17 international meeting. They're very good. Moreover, 18 we've been able to get NIAID and the mycology branch 19 of CDC to come and interact with our members and that 20 has been very helpful and we'd encourage FDA at our 21 next meeting.</p> <p>22 It currently has a board and bylaws,</p>	<p style="text-align: right;">Page 172</p> <p>1 went ahead and did that and working with Mayne, and 2 you heard Gareth, on Suba-itraconazole and UC Davis 3 and University of Arizona Tucson were already working 4 on this.</p> <p>5 We put together a consortium: UC 6 Davis, Kern Medical Center, Mayo Clinic in Arizona, 7 and University of Arizona Tucson, which are all 8 entities that are extremely -- have a long history of 9 interest in coccidioidomycosis and are essentially all 10 referral centers for cocci. And so this served as 11 sort of a model. Could we do this?</p> <p>12 So that may increase the number of 13 studies we can do with this model, but it doesn't 14 answer all the concerns that we have about moving the 15 field forward, getting good clinical data on 16 therapeutics. For example, doesn't provide 17 independent design and statistical support. It's 18 probably not going to look at best management 19 practices, save for primary pulmonary disease.</p> <p>20 It may not be a good mechanism to look 21 at newer drugs or targets, so the idea that G.R. and I 22 are interested in and I've talked to Pete Pappas at</p>
<p style="text-align: right;">Page 171</p> <p>1 but that's a relatively recent development. It is not 2 legally or financially organized. In fact, its money 3 is held by (inaudible) which is the 501(c)(3) at Kern 4 County Medical Center, so we don't hold our own money 5 and we're not organized in any legal manner. And we 6 have never as an entity overseen a research study.</p> <p>7 So why should be involved in this? 8 Because its members and its prominent members have all 9 been involved in designing and doing studies, many of 10 whom have been involved in the original MSG studies. 11 So we have a tremendous amount of expertise.</p> <p>12 So what's the proposal I'm going to 13 make today? Well, G.R. Thompson, one of our members 14 and I think who's on the call proposed to me about a 15 year or two ago, how could be use the cocci study 16 group to design some studies. And I talked to G.R. 17 and in fact said -- went over these issues that we're 18 really not an entity. We really have no funding, but 19 what we had was expertise.</p> <p>20 And the concept we came up with is 21 perhaps we could use our membership to build a 22 consortium and also help design the study. And G.R.</p>	<p style="text-align: right;">Page 173</p> <p>1 MSGERG, is could we go back to the older model where 2 MSG not has a new coccidioidomycosis subgroup, so MSG 3 provides us, again, with that statistical and design 4 support and administrative support that allows us to 5 do studies that are beyond what industry would give 6 us.</p> <p>7 So that's all I have to say and I'll 8 end right there.</p> <p>9 DR. JANIS BLAIR: Thank you very much, 10 Neil. We will -- we have scheduled right now a break 11 and we'll be back at 4 p.m. to start the moderate 12 panel discussion.</p> <p>13 (Break)</p> <p>14 DR. JANIS BLAIR: Never really can tell 15 if everyone is back or not, but I will thank everyone 16 in advance for their participation. We actually have 17 a generous amount of time for this next session and 18 there are three questions that have been posed for our 19 consideration. I will say that for panel members who 20 want to make a comment, it's probably going to be 21 easiest for me to see if you show a raised hand icon 22 and then we will call on you to speak. You can,</p>

<p style="text-align: right;">Page 174</p> <p>1 instead, type something in the Q&A box and we'll try 2 to keep that monitored as well. 3 So the first question that has been 4 given for our consideration is, what are some 5 considerations for drug development with regard to 6 specific populations? For example, but probably not 7 limited to, a varying array of immunocompromised 8 patients, pregnancy, pediatric and other patient 9 groups. 10 DR. JOHN GALGIANI: Janis, I see Tony 11 has his hand up. You want to recognize him? 12 DR. ANTONINO CATANZARO: Yes -- 13 DR. JANIS BLAIR: Yes. Let's start 14 with Dr. Catanzaro, though -- oh, yes. Okay. Yes, I 15 see him. Thank you. 16 DR. ANTONINO CATANZARO: Thank you very 17 much. I want to take the privilege of being an older 18 member to bypass the three questions you've posed and 19 follow up to Neil's presentation which I think was 20 excellent, and that is that we need a mechanism. When 21 we look back, the Mycoses Study Group with a strong 22 core that builds, disputes, and Gretchen Cloud had</p>	<p style="text-align: right;">Page 176</p> <p>1 on those for over a decade. There's a number of new 2 compounds in development, which we heard from today, 3 some of which are, of course, fungicidal, a lot of 4 promise with that with olorofim, you know, its 5 upcoming Phase 3 trials for that compound and I think 6 the others we heard from as well. 7 There's really promise and indication 8 for those. And, you know, we've really built a nice 9 infrastructure that Neil gave a nice overview of. 10 Used to -- and since that, it's even expanded further 11 for some other studies that are planned, UC San Diego 12 is involved in that. UCLA, an enormous medical center 13 will be involved in that as will UCSF, so I -- and we 14 have done some nice collaborative work already which 15 most of you have been authors on. 16 So I completely agree. I think that it 17 would -- we had a successful model for a long time and 18 that really just needs to be sort of set back up in 19 the same fashion it was, the Mycoses Study Group. You 20 know, Bill Dismukes did a fantastic job. Pete Pappas 21 has done also, you know, enviable job as well and 22 Jerry McGlynn has been their statistician there now</p>
<p style="text-align: right;">Page 175</p> <p>1 within the investigators supporting a group of 2 knowledgeable investigators, but the point I want to 3 make is that none of the studies they did were without 4 the contribution of industry support. 5 So we have the combination of a strong 6 core, knowledgeable investigators, and industry all 7 working together under one goal. And I think that 8 that model worked very well for MSG and really needs 9 to be reinitiated in this critical time when we have 10 not only vulnerable populations but also a number of 11 drugs that need to be studied. 12 DR. JANIS BLAIR: Thank you, Tony. 13 Does anyone want to follow up on Dr. Catanzaro's 14 statement? George Thompson. 15 DR. GEORGE THOMPSON: Yeah, can you 16 hear me okay? 17 DR. JANIS BLAIR: Yeah. 18 DR. GEORGE THOMPSON: Yeah, I would 19 echo that. I mean the Mycoses Study Group in 20 conjunction with the cocci study group was very 21 successful and Tony gave a really nice overview of 22 those studies, and then we, honestly, sort of coasted</p>	<p style="text-align: right;">Page 177</p> <p>1 for a number of years with numerous Mycoses Study 2 Group studies, so I think that the existing 3 infrastructure just seems to be leveraged to move this 4 forward in rapid fashion. 5 DR. JANIS BLAIR: Thank you, G.R. I 6 think I see Dr. Johnson, Royce Johnson. 7 DR. ROYCE JOHNSON: Yeah. To go back, 8 I certainly agree with what Tony and G.R. said, but to 9 go back to the question about doing studies in immune 10 incompetent populations if I, for formulate it, 11 meaning pregnant individuals maybe that are on immune 12 modulators, so forth. I think -- but Janis, you might 13 be better to answer this question than I, that the 14 numbers of those patients is too small to construct a 15 meaningful study for therapy. It's conceivable that 16 there could be prophylaxis studies. 17 DR. JANIS BLAIR: Yeah, I'm not sure. 18 I think you're right on some of the populations being 19 very, very small, probably too small to do any kind of 20 efficacy, but I think we actually have some fairly 21 substantial groups within immunocompromised patients in 22 that there's a fair amount of solid organ transplant.</p>

<p style="text-align: right;">Page 178</p> <p>1 Again, treatment is a thing, but also I think 2 prophylaxis, prevention studies would also be very 3 helpful as well. 4 DR. JOHN REX: Yeah. So pick up on the 5 theme of those populations. They will be -- you won't 6 get terribly many of them in any given -- actually, 7 clinical trial disease, but you can do a lot with 8 developing data to show that your PK is constant 9 across those groups, show that you -- however you're 10 dosing, you want to show that it works in the various 11 populations. 12 You need to be ready for DDI issues. 13 That's very standard work today on Phase 1 healthy 14 volunteer stuff and silico modeling, you can know and 15 be ready to study your DDI issues and actually have 16 them well established and do your special pops work, 17 your hepatic and renal failures well. 18 A lot of this just boils down to 19 reasonably standard, preclinical safety work and just 20 standard Phase 1 studies. And while I'm on the theme 21 of the preclinical studies, one of the hard things in 22 this space for everybody to be aware of is cocci will</p>	<p style="text-align: right;">Page 180</p> <p>1 We have presumed that expression of 2 cellular immunity, thereby skin test or cytokine 3 release, tells us something we -- someone's protected, 4 but we actually don't know that and again, that would 5 be another area of study that, again, industry, 6 pharmaceutical isn't maybe so interested in but as a 7 general area, what are the biomarkers of protection 8 because we actually don't have as much data on that to 9 be confident. 10 DR. JANIS BLAIR: Thank you for your 11 comment. I see a raised hand with Dr. Bennett. 12 DR. JOHN BENNETT: I'd like to turn to 13 the subject of outcome, and we've already heard how 14 difficult it is to measure outcomes in a disease that 15 has different manifestations. But one of the things 16 that all of them have in common is that we want our 17 drugs to make people feel better and function better, 18 and although Royce Johnson and John Rex have already 19 raised this, I want to raise the possibility that we 20 could do this with an iPhone -- a cellphone app. 21 That is, we could send people an email 22 and over the long course that we're treating them, we</p>
<p style="text-align: right;">Page 179</p> <p>1 be treated for a long time. That means that you've 2 actually got to do extended duration safety tox 3 studies and those take a long time and you can't just 4 set off a study, be a nine-month safety tox because 5 you don't really know enough to know how to set that 6 up. 7 So there is a real stumbling block for 8 getting compounds going to achieve the, I guess, to 9 achieve flight here. You've actually got -- there's a 10 whole bunch of background work that is generally 11 invisible that has to be done. Over. 12 DR. JANIS BLAIR: Okay, we'll call on 13 Dr. Ampel next. 14 DR. NEIL AMPEL: Yeah, thank you, 15 Janis. I'm actually going to take on question three 16 because I think it has some relevance. This is 17 something we discussed in the very excellent vaccine 18 meeting we had, I think March a year ago in Rockville, 19 and we do have serology as a biomarker, but we know 20 it's imperfect and there's been a lot of interest in 21 measuring cellular immunity but as I pointed out in 22 that meeting, is it's really an unknown unknown.</p>	<p style="text-align: right;">Page 181</p> <p>1 could ask them to respond. Now, the challenges are if 2 you're sick, you don't want to do anything that's 3 longwinded and we don't want it to be complex. It 4 needs to be in language that's appropriate, but we 5 need that kind of outcome data and I -- there's a 6 model for this and that is in multiple sclerosis, they 7 developed an app that they set up by email to see how 8 people are functioning. 9 Now, they don't ask them how they're 10 feeling, but I think that's important, too, because 11 they want to know if the person's multiple sclerosis 12 functioning is better and I think with that kind of a 13 model in mind, it's a challenge, but it might be a way 14 of getting long-term outcome that is meaningful to the 15 patients. That's the end of my comments, Janis. 16 Thank you. 17 DR. JANIS BLAIR: Thank you, Dr. 18 Bennett. Calling on Dr. Galgiani. 19 DR. JOHN GALGIANI: Yeah, let me make a 20 couple of comments regarding the discussion about 21 immunocompromised and other small groups and also John 22 Rex's concern, a valid concern, about the length of</p>

<p style="text-align: right;">Page 182</p> <p>1 these courses of treatment. We have in the past just 2 decided to allow immunocompromised patients and 3 pregnant patients enroll in the studies -- I could be 4 wrong about some of them, but I think in general that 5 was the case -- and let the investigator or the 6 practicing clinician make the decision about that, and 7 in addition, in early studies, and I'd really be 8 interested to know if the FDA wants to make some 9 comments about this.</p> <p>10 We -- when Dave Stevens and I were 11 doing things like intravenous miconazole, we would 12 start treatment with, you know, not months and months 13 of toxicology in support of that, but rather maybe a 14 month, and then as we got to the end of that, we would 15 report back to the FDA that things were going 16 favorably. We -- the patient was not having untoward 17 reactions of if they were, what they were, and ask 18 permission to continue on and sort of bootstrap as we 19 go for long-term toxicity studies.</p> <p>20 And I'm very interested to know if, for 21 instance, pediatrician -- or pediatrics could be 22 enrolled under that risk-benefit, even though</p>	<p style="text-align: right;">Page 184</p> <p>1 define what that means, and then subject those 2 failures to one of the drugs that we've been talking 3 about. I think that would be a good model to at least 4 talk about.</p> <p>5 DR. JANIS BLAIR: Okay, I'm seeing only 6 raise hands of people who have recently spoken, so I'm 7 not sure if you have another point to make or if you 8 forgot to un-raise your hand, so we'll circle back to 9 Neil.</p> <p>10 DR. NEIL AMPEL: No, I was un-raising 11 my hand, Janis. Sorry.</p> <p>12 DR. JANIS BLAIR: Un-raise your hand 13 then, okay? What about Dr. Bennett?</p> <p>14 DR. JOHN BENNETT: Well, I've been 15 hearing what people are saying about the difficulty in 16 studying this disease and one of the problems that I 17 see is that these people come into the trials at 18 different points in their treatment and that's almost 19 an unsolvable, so haven't heard people address that 20 except for the thought of having people that are after 21 they failed 1,000 milligrams of fluconazole, but I'm 22 concerned they're bringing people in at different</p>
<p style="text-align: right;">Page 183</p> <p>1 pediatric safety had not yet been established if, in 2 the judgment of all involved though that that was in 3 the patients' best interest or not, or whether or not 4 you'd really have to have the Phase 1 done for these 5 groups before you could get them enrolled.</p> <p>6 DR. JANIS BLAIR: Do we have anybody on 7 the panel that can address that?</p> <p>8 DR. ANTONINO CATANZARO: This is Tony 9 again. Can I make a comment?</p> <p>10 DR. JANIS BLAIR: Yes, you may.</p> <p>11 DR. ANTONINO CATANZARO: So I want to 12 go back to question number one and while I agree with 13 you that any one of those groups that are listed are 14 tiny and not subject to -- could not really support a 15 controlled trial, the group that we have a substantial 16 of, as everyone knows, fluconazole at 1,000 milligrams 17 per day is like the community standard, even though 18 it's never been studied. But there are some people 19 who fail that.</p> <p>20 And what to do with the failures is a 21 complete mess. So we could study that group, that 22 sizeable group of people who fail fluconazole, we</p>	<p style="text-align: right;">Page 185</p> <p>1 phases in the trial is -- gives you very heterogenous 2 patient population, so I don't know how to solve that 3 problem, I'm just worrying about it. That's the end 4 of my comment, Janis.</p> <p>5 DR. JANIS BLAIR: I agree with that. 6 It makes it very difficult to understand a result. 7 John, have you got a follow-up comment -- Dr. 8 Galgiani?</p> <p>9 DR. JOHN GALGIANI: Well, I'm -- 10 Sumathi, you're on the call. Is there somebody at the 11 FDA that could give us some thoughts about the Phase 1 12 package that's needed to address small groups? Or 13 people going to take longer than the Phase 1 data 14 really supports?</p> <p>15 DR. JANIS BLAIR: Yeah, I'll defer to - 16 - oh, go ahead.</p> <p>17 DR. SUMATHI NAMBIAR: I can take the 18 call. Hi, Dr. Galgiani. My name is --</p> <p>19 DR. JANIS BLAIR: Hi.</p> <p>20 DR. SUMATHI NAMBIAR: --- division of 21 anti-infectives. So in terms of the pre -- 22 nonclinical data package that is required to support</p>

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<p>1 the studies, I think takes into consideration many</p> <p>2 factors and what types of toxicities we've seen in the</p> <p>3 nonclinical studies, what might be the duration of the</p> <p>4 Phase 1 studies. You know, we can have single-dose</p> <p>5 studies or we can have multiple-dose study, so the</p> <p>6 duration of the non-clinical studies that are needed</p> <p>7 to support each of these studies generally follow what</p> <p>8 is in the ICH accounting and then there is also</p> <p>9 additional requirement in terms of marketing</p> <p>10 applications, for example, for longer treatment</p> <p>11 durations of 13 weeks, for purpose of the clinical</p> <p>12 trial, the 13-week nonclinical study might suffice,</p> <p>13 but for marketing application, there might be need for</p> <p>14 six- or nine-month studies.</p> <p>15 So I think a lot really depends on the</p> <p>16 compound. It depends on what we know about the class</p> <p>17 of the drug, what kinds of toxicities we've seen, were</p> <p>18 they monitorable toxicities, whether they could be</p> <p>19 mitigated with measures in the protocol, et cetera.</p> <p>20 In terms of pediatric, again, a lot</p> <p>21 really depends on the molecule. Sometimes, we do</p> <p>22 require studies in juvenile animals before going to</p>	<p>1 ways we recruit new patients is somebody that wasn't</p> <p>2 doing well.</p> <p>3 And again, I'm -- despite John Rex and</p> <p>4 Jack Bennett, both of whom I much admire, I think that</p> <p>5 having a score system that tells you how sick a person</p> <p>6 is and whether they improve or don't improve that</p> <p>7 score solves the problem of heterogeneity to some</p> <p>8 substantial extent. So you could set a certain score</p> <p>9 and we had, actually, I didn't talk about it today,</p> <p>10 thought that the minimum requirement to be enrolled in</p> <p>11 a trial with the MSG 2020 would be something like a</p> <p>12 score of 6 so that a 50 percent reduction means you</p> <p>13 had to drop 3 points.</p> <p>14 And whether the person's been on</p> <p>15 therapy and failed fluconazole and has a score of 12</p> <p>16 and we drop it to 6 or whether they've never been on</p> <p>17 treatment and they have a score of 12 and we drop it</p> <p>18 to 6, both of those are a success and it's a way of</p> <p>19 dealing with a heterogenous population.</p> <p>20 DR. ANTONINO CATANZARO: This is Tony.</p> <p>21 Can I make a comment?</p> <p>22 DR. JOHN GALGIANI: Go ahead, please,</p>
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<p>1 clinical trials in children, but that's not always the</p> <p>2 case.</p> <p>3 It should be based on all the</p> <p>4 information we have with the nonclinical studies and</p> <p>5 the findings in adult, and then we make an overall</p> <p>6 benefit-risk assessment and decide how to proceed, so</p> <p>7 unfortunately, I cannot give you a particular -- a</p> <p>8 specific answer to your question, but yes, there is</p> <p>9 some degree of flexibility but we have to take into</p> <p>10 consideration all the factors and all the evidence</p> <p>11 before we decide whether it's a go or no go. So I</p> <p>12 hope that helps.</p> <p>13 DR. JOHN GALGIANI: Thank you very</p> <p>14 much. Janis said she's having a little trouble seeing</p> <p>15 names, so maybe I'll -- Royce, are you asking another</p> <p>16 question or making another comment?</p> <p>17 DR. ROYCE JOHNSON: Yeah, I am. As</p> <p>18 regards the heterogeneity issue, I think that can be</p> <p>19 dealt with. All of us that are seeing patients in a</p> <p>20 tertiary sense, which is most of the people that are</p> <p>21 talking, see people that have been on previous</p> <p>22 treatment and failed. In fact, that's one of the main</p>	<p>1 Tony.</p> <p>2 DR. ANTONINO CATANZARO: Well, I agree</p> <p>3 with Royce. I think by far the most common patient</p> <p>4 that is seen by the members of the cocci community of</p> <p>5 -- I don't know exactly what to call them, specialists</p> <p>6 or whatever, by far the most common referral is people</p> <p>7 who failed on fluconazole. So I agree with Jack,</p> <p>8 they're going to be heterogenous. But I think that if</p> <p>9 we shoot for the population that's never seen drugs,</p> <p>10 we'll have the same problem that we had with the FLEET</p> <p>11 study. We're going to be -- we're not going to enroll</p> <p>12 many patients. The majority of the patients that we</p> <p>13 see are people who failed 1,000 milligrams of</p> <p>14 fluconazole and we can "standardize" them, as it were,</p> <p>15 by doing a grade -- score, a Mycoses Study Group</p> <p>16 score, expanded score to pick up these other factors</p> <p>17 and then look for reduction. That was the rationale</p> <p>18 for the original study that Mycoses Study Group did</p> <p>19 which seemed to work very well.</p> <p>20 And then with those failures, then we</p> <p>21 could do multiple therapeutic regimens. We could take</p> <p>22 one at a time and compare continuing 1,000 milligrams</p>

<p style="text-align: right;">Page 190</p> <p>1 with itra, with voriconazole, with one of the new drugs, or we 2 could compare it with an azole versus a new drug, 3 which is what I would like to say -- what I would like 4 to recommend, but the point is that the patient 5 population which is problematic, which needs to be 6 solved, which we have plenty of, people who failed 7 1,000 milligrams. 8 DR. JOHN GALGIANI: Thanks, Tony. 9 Neil, is your hand up? 10 DR. NEIL AMPEL: Yeah, it is, John. I 11 wanted to swing it back to the concept of bringing the 12 MSG in and I know Donna Love is on and I thought I saw 13 Dennis Dixon and Pete Pappas, and I wondered if NIAID 14 or even FDA wants to make some comments about giving 15 government support to cocci studies in addition to 16 industry support, and if Pete's still on, what he 17 thinks of that idea. I'm done. 18 DR. DENNIS DIXON: Well, Dennis is 19 here, while we're waiting for Pete to hear his 20 proposal. And so MSG was really, I think, a model. 21 Was on an island committee for public-private 22 partnerships and how well they worked from 1978</p>	<p style="text-align: right;">Page 192</p> <p>1 exceedingly hard trying to find the company support 2 and a design of the protocol that everybody liked. 3 And I think we had three different names associated 4 with one company with purchases, takeovers, and 5 changes of protocol and the five years ran out before 6 we got to the study. 7 So I think we began to look at the 8 return on the investment and recognizing that 9 diagnosis was such an issue there, shifted and 10 invested and tried to have a better diagnostic for 11 invasive aspergillosis and created a contract to 12 address that. 13 And as we collected the samples, it can 14 essentially be a one-stopping for the clearance of a 15 company for an FDA use for invasive aspergillosis, we 16 could not entice big companies to want to touch that 17 and it's sort of what John Rex described yesterday -- 18 he may want to follow up on this again since not 19 everybody was on yesterday's call -- about the huge 20 challenge, not just getting the Phase 3 done, but 21 having that drug get licenses and sustain its return 22 on investment over the next five-year period and how</p>
<p style="text-align: right;">Page 191</p> <p>1 forward addressing many of the questions people needed 2 to use available drugs effectively. 3 And, as has been said, even the cocci 4 studies, I counted 12 of them, and the ITRA versus FLU 5 was the largest and it was the only one that was a 6 randomized prospective controlled trial and even with 7 that and nearly 200 patients, it did not reach a 8 statistical significance for the primary endpoint, so 9 they're all hard, but beyond that, as we moved farther 10 into the '80s and into the '90s and crossed over into 11 the next century, the model began to collapse because 12 of the disproportionate investment of the government 13 versus pharma and because of the changing landscape 14 for the conduct of clinical trials, the expectations, 15 the rigor, and so forth, and the reluctance of 16 industry to contribute the same amount of money when 17 they could go off on their own and fund it with a 18 design that they preferred. 19 So the last iteration, the last five 20 years of the MSG which was then relabeled the 21 Bacteriology Mycoses Study Group, was the top 22 priority, invasive aspergillosis and people worked</p>	<p style="text-align: right;">Page 193</p> <p>1 the last five drug companies that tried that for 2 antibacterials have now gone bankrupt. 3 So we're very concerned about that and 4 about the time we shifted with the MSG to another way 5 to do business, we made big shifts in the entire 6 division for making Phase 1 the point of handoff to 7 corporate sponsors. And so that way, we could do more 8 things for more microbes and we are doing it in a way 9 that may not be familiar to the cocci community of 10 old, and they're the things that Erin Zeituni talked 11 about this morning where we have compartmentalized it 12 into significant support, probably more than we gave 13 to the MSG, in terms of all the preclinical services, 14 to bring as many new compounds forward as possible and 15 Phase 1 to do first in human hoping that that could be 16 moved along for corporate investment, which is 17 ultimately going to be essential to get the drugs 18 licensed. 19 And then, there are the opportunities 20 for the community to come in with investigator 21 initiated clinical trials, to propose their own in 22 partnership with the community. And we're approaching</p>

<p style="text-align: right;">Page 194</p> <p>1 the in-depth study of the cocci population through the 2 initiative that Donna just sent the community notice 3 of, and that is those consortiums to study cocci 4 patients in clinical perspective and invasive 5 perspective to try and get out some of the very things 6 this group is discussing.</p> <p>7 So I think I'll call your attention 8 back to the link for that initiative for groups to 9 work together collaboratively to study in depth cocci 10 patients and look at how you can leverage that 11 information to move forward to a clinical trial. 12 John, do you want to add anything, John Rex, to nature 13 of the problem in antimicrobial development in general 14 today?</p> <p>15 DR. JOHN REX: Yeah, sure, Dennis. 16 Thanks. The broad problem is that antibacterials, 17 much more so than antifungals -- antifungals pick it 18 up a little bit as well -- suffer from a real market 19 failure problem. It's the antibacterials, antifungals 20 are space where you invent a new drug, everyone's very 21 proud of you and pleased and tells you it's an 22 important thing to do. As a matter of fact, it's so</p>	<p style="text-align: right;">Page 196</p> <p>1 the antifungal universe and has been the subject of a 2 lot of work, and I don't mean to be self-serving, but 3 if you want to learn about it, one way to do it would 4 be to go to my website, AMR.Solutions. there's a 5 newsletter that I put out.</p> <p>6 I spend 20, 25 percent of my time 7 dealing with this problem, sort of on a very broad 8 global scale and there's been a lot of work. There -- 9 legislative activities, there's some stuff going on in 10 the U.K. where we have laid out the framework for what 11 needs to be done to cause drugs to come onto the 12 market and stay on the market. The story of cocci is 13 just, in many ways, is a microcosm of the larger 14 problem, antibacterial.</p> <p>15 So thanks, Dennis, for calling that out 16 and I think it's -- the reason it's important for the 17 community to know about it, you can leverage it, you 18 know. To the extent you can connect the story here to 19 the kinds of solutions being used, it actually helps 20 all of us because our political leadership has been 21 being updated, but they've begun to learn these ideas 22 and if you learn to speak to them using the language</p>
<p style="text-align: right;">Page 195</p> <p>1 important that we're not going to use it and -- unless 2 we really, really, really have to.</p> <p>3 That doesn't work well for the over -- 4 for keeping a product on the market and the -- an 5 insight that's kind of glaringly obvious in 6 retrospect, just like lots of things, is that initial 7 approval of a new drug is really only about 40 or 50 8 percent of the way into the lifetime of the drug, and 9 you need several hundred million dollars beyond the 10 point of approval to simply stay in business, keep the 11 lights on, and stay -- break even on a cash flow 12 basis.</p> <p>13 A vivid demonstration of this is that 14 of the last 15 drugs approved by the FDA in 15 antibacterial spaces, about 2009, five of them are now 16 -- their company is in bankruptcy and the -- or the 17 equivalent thereof, and the availability of the drug 18 is uncertain. Indeed, it seems not likely that you 19 can get it right now.</p> <p>20 So it is a -- this need to deal with 21 the backend problem of sustaining new products in the 22 market is a bigger problem than might appear from just</p>	<p style="text-align: right;">Page 197</p> <p>1 that we have developed over time about antimicrobials 2 as being the fire extinguishers of medicine, 3 antimicrobials as preparedness, COVID gives us a great 4 lesson here.</p> <p>5 You know, a year ago, no one would've 6 paid anything for an anti-SARS, coronavirus drug, but 7 now people would pay trillions of dollars. So there's 8 a lot of really good lessons here for the community to 9 pick up on. Over.</p> <p>10 DR. DENNIS DIXON: A lot of the -- 11 DR. JOHN GALGIANI: Hold on -- 12 DR. DENNIS DIXON: I'm sorry, is that 13 --</p> <p>14 DR. JOHN GALGIANI: Was that Pete that 15 wanted to make a comment? Don't hear him. I would 16 like to maybe think about the biology here. I think 17 there's some good news about the dimorphics in cocci 18 in particular that probably, if we found a better drug 19 for cocci, it would not be put on the shelves. We 20 would be using it because -- for a couple reasons. 21 One is, we need it. And the other is because I don't 22 think that you acquire resistance to drugs in the</p>

<p style="text-align: right;">Page 198</p> <p>1 dimorphics like you do in transplant units where 2 you're doing a lot of prophylaxis or ICUs where you're 3 selecting new colonizing organisms. 4 I think cocci is a point source 5 infection and you're left with that infection until 6 you control it and so it's hard for that fungus to 7 develop resistance in a closed space, and so I think 8 there would be lots of reasons to encourage use of 9 better therapies if they were developed for cocci. 10 But the point that Dennis was making in 11 terms of getting buy-in from industry, I would like to 12 see -- and I think that's for prophylaxis studies or 13 empiric trials has its own special set of issues, but 14 in terms of industry being willing to work with the 15 investigators and allowing the design to emerge 16 through an honest broker like MSG, with the analysis 17 being done by the statistical support of the central 18 group for cocci, would that be actually an easier 19 problem than to try to figure out how to model or 20 posture a indication for the immunosuppressed patient 21 populations? 22 Anyone have some thoughts about that?</p>	<p style="text-align: right;">Page 200</p> <p>1 you on each of those points, including the submission 2 of trials. 3 And visit our resources in our webpage 4 for opportunities in the area. 5 DR. JOHN GALGIANI: But Dennis, the 6 wonderfully exciting idea for cocci centers coming 7 forward, I am so looking forward to that process play 8 out, but can I ask you, that you have been -- when you 9 roll things back to Phase 1, why not reexamine that, 10 whether or not you want to allow for some diseases -- 11 and I would like to think we'd be talking about cocci 12 -- that it wouldn't stop at Phase 1, that you could -- 13 I could imagine some really interesting Phase 2 trials 14 with adaptive designs that would be cutting edge that 15 would be, you know, we move the field forward in 16 design as well as getting some results. 17 What about that as being either -- the 18 cocci centers, as I understand it -- I haven't seen an 19 RSA yet, but I believe it's going to not support 20 clinical trials. It may collaborate with others doing 21 clinical trials, but you're not going to be -- funding 22 budget for the clinicals within the centers</p>
<p style="text-align: right;">Page 199</p> <p>1 Neil. 2 DR. NEIL AMPEL: Well, John, I don't 3 have thoughts, but I want to throw it back to Dennis. 4 So, Dennis, I heard what all the problems were but 5 following up on John, so what is our solution, because 6 we don't have, at this time, really well-designed, 7 well-controlled trials and I think everyone has spoken 8 today how difficult that would be simply with industry 9 support. 10 So what mechanism, if not 11 reinvigorating MSG to assist in that, what mechanism 12 might you use? Over. 13 DR. DENNIS DIXON: Okay, I have the 14 name of that group, so I would start with the 15 Coccidioidomycosis Collaborative Research Centers 16 which are listed on concepts cleared web page with 17 NIAID as a simple couple sentence explanation about 18 them, the whole thing won't be public until we are 19 finalized, posted for advertisement, and I would 20 suggest you call in to me, to Erin Zeituni, to Baoying 21 Liu or any of the others associated with this meeting 22 to tell you what opportunities we have to work with</p>	<p style="text-align: right;">Page 201</p> <p>1 themselves. 2 DR. DENNIS DIXON: The norm is now 3 Phase 2s. There are exceptions. I think with 4 something like the collaborative research centers, the 5 intent is to have people dig down to solve some of 6 these problems where there could maybe be something 7 too good to leave sitting at the curb. 8 DR. JOHN BENNETT: Will there be strong 9 active input into that decision-making process? 10 DR. DENNIS DIXON: Could you repeat 11 your question? 12 DR. JOHN BENNETT: That concept sounds 13 really good from a governmental point of view. I just 14 wonder if we're kind of thinking about the benefit of 15 the Mycoses Study Group, one of the strong benefits 16 was the intimate relationship that included clinicians 17 and academics in the decision making process. And I'm 18 wondering if that's going to be part of the program 19 you're planning. 20 DR. DENNIS DIXON: We really can't 21 comment on what it's going to be other than what's 22 been posted on the web, and then when the solicitation</p>

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<p>1 is published, it will say exactly what it's about.</p> <p>2 DR. JOHN BENNETT: Well, I'm just</p> <p>3 thinking about the FLEET project and how it</p> <p>4 originated. And Dennis was intimately involved in</p> <p>5 that and it was a wonderful "gift" to the community of</p> <p>6 \$10 million, but the decision making process in</p> <p>7 bringing that study from the \$10 million to actually</p> <p>8 doing it, did not -- it had academic input, but it</p> <p>9 didn't -- it was not effective input. And I think</p> <p>10 that the result of that was not successful.</p> <p>11 DR. DENNIS DIXON: Well, thanks for</p> <p>12 that opinion.</p> <p>13 DR. JOHN GALGIANI: But Dennis, what I</p> <p>14 hear, if I understand you correctly, you're saying</p> <p>15 that if somebody had an idea for a Phase 2, that the</p> <p>16 policy is not so rigid within DMID that it couldn't be</p> <p>17 discussed, with the possibility it might actually be</p> <p>18 explored.</p> <p>19 DR. DENNIS DIXON: I think that's a</p> <p>20 safe statement. That's what we mean by case-by-case</p> <p>21 decision making and certainly, look where COVID went.</p> <p>22 Nothing is exactly like COVID, thank goodness.</p>	<p>1 DR. JOHN GALGIANI: Tom? Good. You've</p> <p>2 been intimately involved, as we heard, with doing the</p> <p>3 animal studies on various antifungals for development</p> <p>4 for NIAID. Do you want to make any comments about how</p> <p>5 successful that process has been and do you think it</p> <p>6 could be done differently or are you happy with the</p> <p>7 way it's set up?</p> <p>8 DR. TOM PATTERSON: It has been a very</p> <p>9 successful partnership. I think it's really helped</p> <p>10 spur drug development and I think you heard from our</p> <p>11 industry partners in those earlier talks that those</p> <p>12 studies were able to give pretty critical data that</p> <p>13 would otherwise be maybe outside their range at this</p> <p>14 point in time with their development, so cocci</p> <p>15 would've kind of gotten kicked to the curb. And</p> <p>16 instead, they really got a real boost when they were</p> <p>17 able to show activity in those models. And so I think</p> <p>18 it was an example of where the preclinical investment</p> <p>19 by the NIH was able to really spur drug development.</p> <p>20 And I think the same things can</p> <p>21 continue with even smaller companies moving forward,</p> <p>22 you know, and so we'll have to see how much support</p>
<p>Page 203</p> <p>1 DR. NEIL AMPEL: So Dennis, this is</p> <p>2 Neil. Just to come back, the problem I have with the</p> <p>3 cocci collaborative groups doing broad pharmaceutical</p> <p>4 studies, let's just say the RFA comes out to</p> <p>5 University of Arizona has one and UC Davis has one.</p> <p>6 To me, that's not solving the problem, because those</p> <p>7 are going to -- that's siloing the problem where we</p> <p>8 really want all those medical centers involved, so if</p> <p>9 we're going to do therapeutic trials, we want every</p> <p>10 center that sees cocci patients and particularly those</p> <p>11 that are very involved, and I guess that's why I'm</p> <p>12 having trouble. I don't see that as the solution to</p> <p>13 the problem.</p> <p>14 DR. DENNIS DIXON: There's nothing more</p> <p>15 I can give you at this point because the policy of the</p> <p>16 division is what it is and we'll work with you any way</p> <p>17 we can to move things forward iteratively.</p> <p>18 DR. JOHN GALGIANI: I'm noticing that</p> <p>19 there's a lot of people on this panel, many of whom</p> <p>20 haven't said much yet. Tom Patterson, are you there?</p> <p>21 Maybe not.</p> <p>22 DR. TOM PATTERSON: Hello.</p>	<p>Page 205</p> <p>1 that continues. It's important for the community to</p> <p>2 reach out to the government and let them know that</p> <p>3 they find it useful, but I think it is an important</p> <p>4 process to do and has really been helpful so far in</p> <p>5 getting drugs moved ahead, and even in the regulatory</p> <p>6 paths, you can -- you heard from, this morning, how</p> <p>7 those could be useful in helping lead to approvals.</p> <p>8 DR. JOHN GALGIANI: Good. I see Dr.</p> <p>9 Hope is logged in. Dr. Hope, are you there? Maybe</p> <p>10 not. I happened to --</p> <p>11 DR. WILLIAM HOPE: Yes, I'm here.</p> <p>12 DR. JOHN GALGIANI: Yes, I see your</p> <p>13 name. You recently were having to grapple with a</p> <p>14 patient with Valley Fever. Was this workshop helpful</p> <p>15 to you in terms of seeing where we could go better?</p> <p>16 DR. WILLIAM HOPE: Well, I'm listening</p> <p>17 from a place that, of course, doesn't see this disease</p> <p>18 except for the one that I mentioned this morning,</p> <p>19 John. I guess the only comment that I have, sort of</p> <p>20 listening to a disease that I don't look after</p> <p>21 previously and I don't study, although I have worked</p> <p>22 with Laura Kovanda and David Stevens recently on the</p>

<p style="text-align: right;">Page 206</p> <p>1 model, but the preclinical models have obviously been 2 truly difficult and characterized by pretty 3 significant variability, but something that I haven't 4 heard all day is that triazoles are the mainstay of 5 treatment of this disease and we know that there's 6 extraordinary variability (inaudible) sort of curious 7 that people haven't been more interested in sort of 8 understanding from a pharmacological perspective why 9 fluconazole fails, why you say it's fungistatic, where 10 the space are that emergence of resistance. I asked 11 them to break out compliance (inaudible) about 12 penetration of these drugs into complex tissue base. 13 So there's seems to be a lot of basic 14 science here that could help unravel some of the 15 issues. There's been quite a clinical discussion all 16 afternoon. So that's, I guess, my only perspective 17 from somebody very much from the outside. 18 DR. JOHN GALGIANI: Thank you. I see 19 John Rex has got his hand up. 20 DR. JOHN REX: Hi. I'm coming off 21 mute. Dennis, coming back to you for a second. I 22 want to think out loud and actually I think that</p>	<p style="text-align: right;">Page 208</p> <p>1 here and I think that's probably a much heavier lift 2 than any of us can envision; whereas, I'm actually 3 struck by the idea that there might be a way to 4 measure things that patients really care about with 5 tools -- there's been a lot of work on these general 6 purpose PROs in the past 10 years. 7 I'm not an expert on it, but I am 8 really quite surprised that -- and it puzzled me how 9 much stuff is out there. So that's a call for maybe a 10 group action. That can be something that would be a 11 big community benefit. Over. 12 DR. JOHN GALGIANI: Yeah, the QID which 13 we heard about earlier today which was -- has been 14 involved, I think, within the FDA and NIH, that is 15 more -- correct me if I'm wrong, those who know more 16 about this -- is more for professionals talking to 17 each other about their experiences. I guess what 18 John's talking about is to get the patient feedback 19 and what FDA -- are they working on that, also or 20 would it need to be a new opportunity rather than the 21 QID. 22 ELEKTRA PAPADOPOULOS: Are you able to</p>
<p style="text-align: right;">Page 207</p> <p>1 Elektra Papadopoulous is on who is somebody I know has 2 thought a lot about PROs, and I'd like to point -- ask 3 the question of whether or not this community could 4 get interested in developing a PRO, focus on how 5 people feel. Maybe it's arm on the phone Jack, that's 6 be fun, but the idea that an endpoint that we all 7 agree is reasonably useful across the range of cocci 8 syndromes would be a tool that everybody would get 9 advantage of it. 10 And Royce, I do really appreciate what 11 the MSG did, what you guys did with the points scoring 12 system. The -- my general understanding in this area 13 is that things like cocci Comp. Fix titer or CSF white 14 count would be new to this category of biomarkers and 15 while you and I as docs pay a lot of attention to 16 them, if we want to use them as endpoints in a trial 17 that enables regulatory action, we'd have to go to a 18 lot of trouble to prove how they connect to the 19 outcome of the disease and like with HIV, where we 20 know what it means to have a certain quantitative 21 viral load. 22 We'd have to do the equivalent that</p>	<p style="text-align: right;">Page 209</p> <p>1 hear me? 2 DR. JOHN GALGIANI: Yes. 3 ELEKTRA PAPADOPOULOS: Oh, great. 4 Okay. Yeah, I did hear my name so I thought I could 5 just chime in a bit from a regulatory standpoint on 6 the patient reports outcome questions and I think 7 we've heard expressed multiple times that our goals 8 with our endpoints is really to assess the clinical 9 benefit on how patients feel, function, and survive 10 and so we know that there's a need for outcomes that 11 are reliable, valid, and responsive and that we need 12 to take into account what really matters to the 13 patients. 14 And that begins with listening to the 15 patients and how do they discuss their condition, the 16 treatment, what are the therapeutic gaps, and what 17 really matters to the patient, what are things that a 18 drug can treat that would impact their disease and 19 also help them to feel better or function better, what 20 would it be that they would most like to see improved, 21 and then really factoring these explicitly into the 22 endpoints.</p>

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<p>1 And I've heard -- there's been a lot of 2 discussion about the challenges of heterogeneity and I 3 think that there is a potential possibly to find 4 certain symptoms that cross individuals that could be 5 relevant across a broad variety of individuals and 6 that patients could self-report so we would have a way 7 of hearing the patient voice and how they're feeling 8 and functioning and to take, really, and say adults 9 and adolescents, those who are able to provide self- 10 report.</p> <p>11 And I think, you know, we've also heard 12 about the length of the trial, the need to be 13 parsimonious in the measures. I think minimizing 14 missing data is also going to be very important, so 15 having something that's feasible, that the patient is 16 indeed compliant with is going to be important.</p> <p>17 And then we've also heard about the 18 need for different language translations for that 19 target population. So it's a lot, I think. I think 20 having some good clinical outcome assessments that 21 could be used to support approval would be a bit boost 22 to drug development.</p>	<p>1 DR. TOM WALSH: Oh, no. Okay. John, 2 are you able to hear me?</p> <p>3 DR. JOHN GALGIANI: I am.</p> <p>4 DR. TOM WALSH: Okay, very good. John, 5 I wanted to comment with regard to preclinical and 6 then also a strategy that might be helpful for 7 support. Number one is, in terms of compounds that 8 seem to be (OVERLAPPING VOICES OBSCURES) at a 9 preclinical level.</p> <p>10 One of the features that seems to stand 11 out is, one, the potential microbicidal or fungicidal 12 activity certainly posaconazole seemed to have that, 13 the large volume of distribution, if we look at the 14 data, certainly that's been presented with olorofim, 15 for example. It seems to be also -- it seems also to 16 have similar properties. One would also imagine that 17 ibrexafungerp, large volume of distribution, 5 liters 18 a program, and also apparently fungicidal.</p> <p>19 Those agents certainly may rise to the 20 level preclinically with appropriate dosing strategies 21 to taking on the most serious patients. And if you 22 look at -- if we look at the most serious patients,</p>
<p>Page 211</p> <p>1 Very often, if there are good outcome 2 assessments and there's regulatory agreement, then 3 that's an incentives for drug development, and so the 4 agency, of course, we will always provide advice to 5 individual companies in the context of their drug 6 development programs and there's also another 7 regulatory pathway for looking at clinical outcome 8 assessments and other drug development tools which is 9 the qualification pathway and so that may be another 10 very good avenue to have a tool that could be reviewed 11 by the agency where we could provide advice and that 12 could be usable across drug development programs and 13 made publicly available and it wouldn't need to be 14 necessarily de novo drug -- a de novo PRO or COA 15 development.</p> <p>16 There could be existing tools that 17 could be brought to bear and so I think it would be a 18 good conversation to have, and I just -- yeah, so I 19 think that concludes my brief remark.</p> <p>20 DR. JOHN GALGIANI: Thank you. I see 21 Tom Walsh has his hand up. Tom? Are you on mute, Dr. 22 Walsh?</p>	<p>Page 213</p> <p>1 which is really where people are devastatingly 2 compromised, the posaconazole trial actually for the 3 salvage study, had 73 percent response rate where 4 patients were just utterly not responding and I think 5 as I recall, about 6 of the 17 had widespread -- had 6 disseminated disease as well.</p> <p>7 So if one has to decide, well, what 8 might be logical extensions, translational from the 9 preclinical data because you only have X number of 10 compounds, the Y number of patients, at least those 11 properties seem to stand out in contrast more to a 12 flu, which -- fluconazole which may not have those 13 properties, but the other consideration, then, is 14 well, who might be interested in supporting when 15 industry obviously as has been wisely stated some 16 degree of reluctance about further support, but there 17 may be some considerable interest in military.</p> <p>18 With all the maneuvers, there is -- 19 Demosthenes Pappagianis' paper came out. He estimated 20 that there may be as much as 4 or 5 percent serologic 21 conversion. Frequency of serious infection was low, 22 but nonetheless there are cases I'm aware of that came</p>

<p style="text-align: right;">Page 214</p> <p>1 out of the -- especially in the armored command -- 2 that came out of training. So I would raise the 3 question, would the military, given its exposure, also 4 maybe CDMRP, the Congressionally Directed Military 5 Research Program, which does offer grants for -- in 6 further support might be interested in clinical trial 7 development. 8 DR. JOHN GALGIANI: Thank you, Tom. 9 Tony Catanzaro and Dave Stevens, I think both of your 10 have had some experience trying to engage with 11 military. Do either of you want to weigh in on that? 12 DR. ANTONINO CATANZARO: I actually 13 have a DoD grant right now but it -- they're very 14 particular. They tell you what they're interested in 15 and then you apply for it and I have a TB grant, but 16 I've never seen anything about cocci. I work closely 17 with the Navy Balboa Center and they had a lot of TB 18 patients and they're interested, but they don't have 19 any funding that I'm aware of. 20 DR. JOHN GALGIANI: Well, we in the 21 formalin-killed serial vaccine, there was a lot of 22 attempts to get military involvement and indeed, the</p>	<p style="text-align: right;">Page 216</p> <p>1 somebody else, but now I'm unmuted. So I wanted to 2 return to how we're looking at the problem and I think 3 when the MSG ended, people wanting MSG back and so the 4 MSG isn't back. There are no plans to bring it back. 5 What is there and is available can do some of the 6 things that group did but not through an 7 infrastructure support basis. 8 So for example, Tony or others who 9 would like to leverage the CSG for particular kind of 10 study, for particular problem, it could be looking at 11 the 1,000 milligram fluconazole failures and putting 12 them into some sort of study that you could do at an 13 early stage clinical investigation. There are new 14 ways to do that; that's why I encourage reaching out 15 to the bacteriology and mycology group team and either 16 have the ways to reach us and so you could write or a 17 group could write a clinical trial planning grant and 18 there's a certain amount of money, up to, I think it's 19 \$150,000 to develop a protocol. 20 So that could be the part where the 21 experts get together, some up with the idea, map out 22 the basics of a protocol. That's competitively</p>
<p style="text-align: right;">Page 215</p> <p>1 Lemoore Naval Hospital was one of the study sites for 2 that vaccine trial in humans. But in general, my 3 experience with the military is that if you don't have 4 -- and this actually is reflecting comments I got from 5 David Danley who was a career military person at Ft. 6 Dietrich that said if the -- if a treatment for Valley 7 Fever or a prevention of Valley Fever is not a written 8 in the requirement in the user's manual for the 9 military, that is if you don't have a requirement to 10 have such a vaccine, in order to have a military, then 11 you're just not going to get any priority. 12 We've had sympathetic interests at 13 regional military bases for periods of time, but then 14 they rotate every two or three years and you start all 15 over again. So I think I could imagine how we could 16 do that with the military, but I haven't seen the push 17 to get it as a military requirement. Dennis. Dennis 18 Dixon, are you there? You had your hand up. 19 DR. DENNIS DIXON: It looks like my 20 line is muted. 21 DR. JOHN GALGIANI: Dennis, are you -- 22 DR. DENNIS DIXON: I was muted by</p>	<p style="text-align: right;">Page 217</p> <p>1 reviewed and funded against all the other people who 2 don't have infrastructures who are trying to do that, 3 and they do get funded and they're successful. 4 After that, if you've got the protocol 5 and it looks like there was traction, there's the 6 option to apply for an investigator initiated clinical 7 trial grant that can conduct probably the kinds of 8 study you're looking at to do, so there are ways to 9 get there if you can work with the system to try them. 10 MAN 1: That's very encouraging. 11 DR. DENNIS DIXON: -- extra layer -- 12 they do work through that extra layer of peer review. 13 It's time consuming and peer review is generally more 14 frustrating than it is gratifying, but it is a way to 15 get there, just like other contract and grant support 16 throughout the NIH. 17 To take a look at the resources that 18 are there. Understand them better and see how they 19 might be used to advance and leverage your interests. 20 The response to standard review and 21 then you work through that, because that's quite 22 stilted in the interactive potential. It's very</p>

<p style="text-align: right;">Page 218</p> <p>1 difficult to work through the standard review process 2 through (inaudible) who have worked with the reviewer. 3 I think that they rotate, so if you use that system or 4 do you use a different system? 5 DR. DENNIS DIXON: A number of these 6 grants have been funded to other groups, bacteriology. 7 I can't remember if we had any recent ones. I think 8 we've had some in mycology, too. Baoying would know 9 that, who spoke this morning. So people do get 10 through it. It's not like having a multimillion- 11 dollar contract aware that you can make all the 12 decision on yourself moving forward; it is a way to 13 go, and it has worked for some people. And it could 14 work for you. 15 DR. JOHN GALGIANI: Dr. Bennett, I see 16 your hand's up. 17 DR. JOHN BENNETT: It seems to be -- 18 can you hear me, John, okay? 19 DR. JOHN GALGIANI: I can. Thank you, 20 John. 21 DR. JOHN BENNETT: Okay. It seems to 22 me the best hope for a cocci drug is to have a drug</p>	<p style="text-align: right;">Page 220</p> <p>1 approved would be primarily for cocci and if that were 2 to occur, then that would open up some post-marketing 3 trials, Phase 4s, to look at outcomes for other 4 diseases. There's also activity assessment in blasto, 5 but I think those are modest markets given the size of 6 the markets and other therapies. 7 But I think the idea of synergy with 8 the azoles -- sorry, with echinocandins, for example, 9 would be an exciting possibility for other diseases 10 besides cocci. But that doesn't -- it's hard to put 11 that into a development plan to get it to its first 12 indication. 13 DR. JOHN BENNETT: So maybe if a drug 14 like olorofim got an indication for treatment or 15 prevention or both of aspergillosis and had a good 16 enough market size, yet its use for cocci could be an 17 important side effect, if you will, but it's not what 18 makes the drug economically viable. It's another 19 indication, but we could still use it for cocci if we 20 could figure out a good way how to study that or some 21 other drug that has a broader indication. 22 DR. JOHN GALGIANI: Dr. Ampel, I see</p>
<p style="text-align: right;">Page 219</p> <p>1 that has broader use than cocci, so that industry 2 support of that drug has to be based upon other 3 indications, but with a well-done cocci study, the 4 drug will also be used for cocci. 5 Approval for cocci, I wouldn't know 6 about that, but the drug isn't approved for -- 7 posaconazole's not approved for cocci, yet you're 8 using it. So the question is, can we have a drug that 9 has broader usage and then we can design a study for 10 cocci that gets people with the knowledge they can use 11 it and here's how to use it for cocci. 12 But I'm a little concerned about drug 13 nikkomycin. If its major use is only for cocci, you 14 need to say that. but if its major use for cocci, I 15 don't know how industry would be able to support that 16 drug. So tell me I'm wrong, John. 17 DR. JOHN GALGIANI: I'm not sure you 18 are wrong. I wish I could tell you you're wrong. But 19 there is evidence suggests that it would be 20 synergistic with other drugs against such things as 21 aspergillus. So the concept that we have sort of 22 entertained primarily is the path to get the drug</p>	<p style="text-align: right;">Page 221</p> <p>1 your hand's up. 2 DR. NEIL AMPEL: John, can you hear me? 3 DR. JOHN GALGIANI: Yeah. 4 DR. NEIL AMPEL: So the question, the 5 two issues. Dennis, the mechanism you proposed would 6 be drug by drug and that really doesn't solve the 7 issue. There might be multiple. We need, really, a 8 mechanism where we can study a lot of drug and if we 9 had to submit for funding drug by drug, I'm not sure 10 that's the solution. 11 The other point I want to make as a 12 clinician, so we all think -- and I talk about this at 13 ID week -- fluconazole is probably not the best drug 14 to use in Valley Fever and the new triazoles seem to 15 be better and we all try every day when we see cocci 16 patients to get them moved over, and the problem is, 17 it's very difficult. 18 For example, TR posaconazole costs on 19 the order of, I think, \$7,500 a month and so 20 frequently requires prior approval, which is 21 frequently denied by insurance companies, so without 22 studies that get us to FDA approval, this was pointed</p>

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<p>1 out before I spoke, it really impacts clinical care</p> <p>2 and it's particularly a problem if we think that</p> <p>3 fluconazole may not be the best drug to use.</p> <p>4 It was just the first drug -- the first</p> <p>5 triazole, anyway, that we used. And so how do we move</p> <p>6 that? We need a mechanism, even for drugs, as Jack</p> <p>7 was saying, that are already available. They're still</p> <p>8 very difficult to use because of our current insurance</p> <p>9 system. Over.</p> <p>10 DR. JOHN GALGIANI: Laura Kovanda, I</p> <p>11 see your hand's up.</p> <p>12 LAURA KOVANDA: Yes.</p> <p>13 DR. JOHN GALGIANI: Hi.</p> <p>14 LAURA KOVANDA: Thank you. I was just</p> <p>15 going to add that it seems like a perfect opportunity</p> <p>16 with multiple different drugs, I guess, in line to do</p> <p>17 studies would a master protocol be an opportunity for,</p> <p>18 say, the Cocci Group or the NIH to pull together,</p> <p>19 including some ideas like John Rex has with the PRO</p> <p>20 type outcomes and a way that could maybe help</p> <p>21 facilitate getting trials done. Thank you.</p> <p>22 DR. JOHN GALGIANI: I don't know if</p>	<p>1 small studies particularly for refractory patients</p> <p>2 where the challenges are especially great or those</p> <p>3 refractory or intolerant, where there's clearly</p> <p>4 tangible benefit, for those patients to be studied in</p> <p>5 a systematic way would not necessarily even have to be</p> <p>6 randomized.</p> <p>7 We talked extensively yesterday about</p> <p>8 refractory historical controls or contemporaneous</p> <p>9 control, so it may be difficult given the wide</p> <p>10 variability, but rather than having extremely --</p> <p>11 relatively large study such as the flu and itra, one</p> <p>12 may be able to understand and use compounds in a much</p> <p>13 more focused way, smaller populations, difficult to</p> <p>14 treat with patients being their own control and</p> <p>15 response much like the posaconazole study where</p> <p>16 potentially in a relatively short span of time, you</p> <p>17 can have potentially great candidates from olorofim to</p> <p>18 ibrexafungerp to other candidates, study in a short</p> <p>19 span of time or a novel study design.</p> <p>20 DR. JOHN GALGIANI: Thank you, Tom.</p> <p>21 Pete Pappas? Are you on mute?</p> <p>22 DR. PETER PAPPAS: -- hear me?</p>
<p>Page 223</p> <p>1 Dennis or Jack, do you still have questions or you</p> <p>2 just didn't put your hand down.</p> <p>3 DR. DENNIS DIXON: -- figure out how to</p> <p>4 do that. My arm's getting tired anyway.</p> <p>5 DR. JOHN GALGIANI: Well, we're a</p> <p>6 little close -- we're about 10 minutes away from the</p> <p>7 allotted time. We have certainly time for additional</p> <p>8 comments. Is that Thomas Walsh?</p> <p>9 DR. TOM WALSH: Yes. Are you able to</p> <p>10 hear me?</p> <p>11 DR. JOHN GALGIANI: Yes.</p> <p>12 DR. TOM WALSH: Sorry, John, it's</p> <p>13 difficult to ascertain as to whether the phone is</p> <p>14 activated. Just in reflection on the refractory study</p> <p>15 -- the refractory cases of posaconazole where large</p> <p>16 challenges, although it may, as was noted, never</p> <p>17 really lead to an indication, but may inform the usage</p> <p>18 and expand the comfort or especially of bolstered by</p> <p>19 adequate preclinical data.</p> <p>20 One might envision if one did have a</p> <p>21 study group that would be, as Laura suggested, a</p> <p>22 universal templated protocol that then could evolve</p>	<p>Page 225</p> <p>1 DR. JOHN GALGIANI: I can now.</p> <p>2 DR. PETER PAPPAS: Okay, good, good.</p> <p>3 I've just been listening to the comments. I'm in</p> <p>4 Montana so it's been kind of in and out.</p> <p>5 DR. JOHN GALGIANI: A little louder,</p> <p>6 Pete?</p> <p>7 DR. PETER PAPPAS: Oh, I'm sorry,</p> <p>8 excuse me. I said I am out state and I'm kind of in a</p> <p>9 remote area, but if you can hear me okay, let me know.</p> <p>10 DR. JOHN GALGIANI: You're kind of</p> <p>11 weak.</p> <p>12 DR. PETER PAPPAS: Yeah --</p> <p>13 DR. JOHN GALGIANI: -- tell you that</p> <p>14 before.</p> <p>15 DR. PETER PAPPAS: Okay --</p> <p>16 DR. JOHN GALGIANI: That's better.</p> <p>17 DR. PETER PAPPAS: People have said</p> <p>18 that before. Is that better? Is that better?</p> <p>19 DR. JOHN GALGIANI: Yeah, that is</p> <p>20 better.</p> <p>21 DR. PETER PAPPAS: Okay, good. Just a</p> <p>22 couple of reflections on this, you know, the comments</p>


<p style="text-align: right;">Page 226</p> <p>1 that were directed to Dennis and all -- and so forth. 2 For - at the risk of being self-serving, obviously, I 3 think that not only cocci but the rest of the fungal 4 pathogens constitute a public health issue and I do 5 believe that one way of getting these addressed is 6 through a uniform group that brings to the table 7 statistical integrity, being -- protocols being really 8 ferreted out in a fashion that we used to do, and I do 9 think, following Jack Bennett's lead and others, this 10 is really a great way to do studies. 11 That said, much has changed in the last 12 decade or so and that is that these -- while we have 13 now lots of compounds, those compounds are oftentimes 14 brought to research through smaller groups, smaller -- 15 venture capitalist groups. They really can't tolerate 16 the delay that is inherent in our traditional way of 17 developing protocols and going through the NIAID and 18 so forth, and so on the one hand, I love the idea of a 19 centrally organized, especially for biostatistical and 20 trial design purpose. 21 On the other hand, I don't know that 22 the tolerance is from industry as to whether they can</p>	<p style="text-align: right;">Page 228</p> <p>1 the time, if anyone else had some additional comments 2 to make, to make them. Are there any shows of hands? 3 I see none. Dr. Stevens. David, are you on mute? 4 DR. DAVID STEVENS: Okay, can you hear 5 me now? 6 DR. JOHN GALGIANI: Really can, loud 7 and clear. 8 DR. DAVID STEVENS: Okay, great. No, I 9 just had a little comment and I thought the discussion 10 about continuing collaborative clinical studies was 11 really most important and I didn't want to in any way 12 divert or interrupt that, but I did have a couple 13 comments about nikkomycin Z. first, we studied nikZ 14 against blastomycosis and published our results and 15 the -- it's a very impressive drug against 16 blastomycosis in the laboratory. 17 And in the course of those studies, we 18 gave huge doses to mice because it was a dose ranging 19 study, and never actually found any toxicity that we 20 could see and I think we were up to, if I can 21 remember, the range of 1,000 milligrams per kilogram. 22 But David Larwood was very modest because currently in</p>
<p style="text-align: right;">Page 227</p> <p>1 tolerate very long delays where things have to go 2 through a series of subcommittees and committees at 3 the federal level, beyond the FDA. So we need to 4 remember that as well. 5 I do think this is a big enough public 6 health issue, not just cocci, but the whole area of 7 mycology in general, that we should be able to justify 8 putting together a study group that at least provides 9 infrastructure in biostatistical support and integrity 10 so that we can help all of these compounds and these 11 entities develop sound studies that really address 12 needs. 13 All of this has been addressed, many of 14 you throughout the day, Neil and others have 15 underscored this but I just wanted to kind of put my 16 two cents' worth in because it's important to remember 17 how we also caused a lot of heartburn on the part of 18 our corporate colleagues who just couldn't wait for us 19 to move forward and we just weren't moving forward 20 fast enough. That's all I wanted to say. 21 DR. JOHN GALGIANI: Thank you, Pete. 22 Well, we're close to the allotted time. This would be</p>	<p style="text-align: right;">Page 229</p> <p>1 our laboratory, we've been studying disseminated cocci 2 which had never been studied before in models with 3 nikZ and David's been very involved in those studies. 4 And it is very active against 5 disseminated cocci as well and although that, unlike 6 the blasto studies, that hasn't been published but it 7 has been presented in part and as an abstract it's 8 available from the cocci study group from the meeting 9 of this year and we've gone on to do some of the kinds 10 of studies that Richard Hector did with CNS cocci and 11 also find it to be very active against central nervous 12 system cocci, and the thing that's different -- I'm 13 sure David would've liked to have mentioned this more 14 -- but maybe he was kind in terms of not trying to let 15 the cat out of the bag, but the dosing has been by not 16 lavaging which is what we did in our published blasto 17 studies, but leaving in the water for -- that the mice 18 are drinking and we monitored how much they were 19 drinking and we could calculate what their dose was 20 based on that and that has been very effective both 21 against disseminated cocci and against CNS cocci and I 22 think where that leads is the possibility of maybe</p>

<p style="text-align: right;">Page 230</p> <p>1 developing a delayed release form which would make it 2 very convenient, get around problems about the half -- 3 any problems that there are about the half-life. 4 So I just wanted to interject that when 5 we were talking about nikZ and hope that's useful 6 information. 7 DR. JOHN GALGIANI: Thank you, David. 8 David Larwood, did you want to add something to that? 9 Unmute? 10 DAVID LARWOOD: Unmute. Hello. 11 Better? 12 DR. JOHN GALGIANI: Much better. 13 DAVID LARWOOD: Sorry about that. 14 Yeah, I actually wasn't going to talk about it because 15 we have some publications that we're developing, but 16 since we're talking about it, Richard Hector did some 17 studies in the last '90s where he used -- infused a 18 rate -- IV infusion of nikkomycin against injected 19 Candida albicans and showed very good results. 20 And so I looked at that and I said, how 21 can we do this in humans. Extended release 22 formulations are very expensive and time consuming to</p>	<p style="text-align: right;">Page 232</p> <p>1 experts that are here, I think the time is right and 2 well poised to bring everyone together, new compounds, 3 great expertise, and the concepts for following Dennis 4 Dixon's path, especially building on the foundation of 5 the exciting idea of the Coccidioidomycosis Centers of 6 Excellence. 7 It would be just a wonderful, logical 8 extension going with the R34s, clinical trial R01s, 9 and with novel study design whether it's in the 10 refractory patients, disseminated CNS, or in advanced 11 pulmonary disease, I think we're on the threshold of a 12 major advance in clinical research in 13 coccidioidomycosis. 14 DR. JOHN GALGIANI: Thank you, Tom. 15 Appreciate those words. And I think we are out of 16 time, so I thank everybody for their comments and the 17 wrap-up will be done by Sumathi Nambiar. Dr. Nambiar 18 is currently the director, Division of Anti-Infectives 19 at the FDA. Sumathi. 20 DR. SUMATHI NAMBIAR: so, thank you, 21 Dr. Galgiani. You can hear me okay? 22 DR. JOHN GALGIANI: Yes, I can.</p>
<p style="text-align: right;">Page 231</p> <p>1 develop and since I'm a chemist working on the 2 molecule, I looked at the properties. I said, I think 3 we can do this dosing in water that David just talked 4 about and it worked. The first experiment worked 5 fabulously well and we're doing some more of these, 6 and like he says, the upper tox limit seems to be 7 unreachable. 8 But the model that I was looking at and 9 it seems to be proving out nicely, is this is a 10 simulation of an extended release formulation, so 11 we're saving a million dollars in a year to just do 12 some screening studies so it's working out quite well. 13 We're anxious to try it in more model diseases. 14 DR. JOHN GALGIANI: Great. And so 15 we're down to the last two minutes. Tom Walsh, do you 16 have any final thoughts you want -- 17 DR. TOM WALSH: Are you able to hear 18 me, John? 19 DR. JOHN GALGIANI: Yes. 20 DR. TOM WALSH: Okay, thank you. I 21 think in listening to all of the outstanding 22 presentations in this vast body of expertise and</p>	<p style="text-align: right;">Page 233</p> <p>1 DR. SUMATHI NAMBIAR: Okay, thank you. 2 I just want to thank all the presenters and panelists. 3 We had a very interesting day discussing different 4 aspects, so coccidioidomycosis. I do have the 5 difficult task of trying to summarize the discussions 6 that took place today. 7 I want to apologize up front if I've 8 missed any of the important points. Meeting materials 9 with recording and transcripts will be available 10 online after the meeting and you should have access to 11 all the details. 12 So today's workshop we had two sessions 13 followed by a very interesting panel discussion. At 14 the first session, we discussed epidemiology, clinical 15 manifestations, and development resources. I think 16 the main points there were about the changing 17 epidemiology of the disease, the risk factors, and 18 disease manifestation and I thought it was also noted 19 that there is an opportunity to here to collaborate 20 with sites outside the U.S. in Central and South 21 America and trial relationships with some of these 22 sites worked well.</p>

<p style="text-align: right;">Page 234</p> <p>1 We had a discussion around animal 2 models. One studied murine models and I think also 3 discussion around rabbit (inaudible). Was also 4 mentioned of the natural pulmonary infection in dogs 5 and I thought that was very interesting, the 6 discussion with enrollment of pets. 7 We had Dr. Zeituni presented the 8 support that NIAID can provide and a lot of this came 9 up a lot of this came up again during the panel 10 discussion. Dr. Zeituni described the established 11 mechanisms available to support the development of 12 promising products and also mentioned the initiated 13 with Coccidioidomycosis Collaborative Research Centers 14 which was discussed by Dr. (inaudible) during the 15 panel discussion and Dr. Zeituni also provided 16 instructive examples of engagement with pharmaceutical 17 sponsors helping to advance drug development. 18 A sincere thanks to Mr. Purdie for 19 having joined us for this workshop and represented the 20 patient. It was a very important discussion and Mr. 21 Purdie highlighted the importance of including the 22 patient's voice and use the patient centered endpoint</p>	<p style="text-align: right;">Page 236</p> <p>1 colleagues from industry and collectively their 2 perspective raised some concerns such as difficulties 3 in actually conducting these trials with regard to 4 identifying and enrolling patients, the need for the 5 long duration of follow-up, et cetera. 6 It was mentioned potential use of the 7 PROs with an endpoint. David raised the concern about 8 financial constraints including the small market base 9 and then there was also a call for potentially 10 streamlining clinical development programs. 11 Dr. Ampel discussed the cocci study 12 group consortium which could potentially help the 13 cocci related treatment study, but said he cannot 14 address all aspects of cocci drug development and 15 presented a proposal for future collaboration to 16 design and implement treatment trials for cocci. 17 The panel discussion was, again, very 18 interesting. We had three questions, but needless to 19 say, the discussions went way beyond those three 20 questions, which is fine, because I think all the 21 points raised were very valid. 22 If I can at really high level</p>
<p style="text-align: right;">Page 235</p> <p>1 to capture how a patient feels, functions, and 2 survives, a theme that came up again during our panel 3 discussion and also the importance of measuring a 4 quality of life. A point he made that I thought was 5 interesting was the potential opportunity to harness 6 the rich database of patients they have access to that 7 we could use to advance endpoint development. 8 In Session 2, clinical trial 9 considerations for the treatment of 10 coccidioidomycosis, we heard about regulatory 11 considerations into the trial development endpoint and 12 available incentives for the treatment of 13 coccidioidomycosis. 14 We heard about trials that have been 15 conducted over the years by the Cocci Study Group and 16 also the lessons learned from the nikkomycin Z 17 development program. 18 For future trials, the discussion 19 around the use of patient reported outcomes and maybe 20 scoring systems at end points. Dr. Johnson discussed 21 the MSG 2020 scoring system with one each for 22 meningial and nonmeningial disease. We heard from</p>	<p style="text-align: right;">Page 237</p> <p>1 categorize, really, to topics, the discussion around 2 pros and cons of having the Mycoses Study Group model. 3 I think there were differing opinions on that with -- 4 opinion that had served us well and is a good model to 5 move forward, understanding that over time the needs 6 have changed and there might be a need to revisit and 7 make some adjustments to that approach. 8 With regard to special population, 9 there's a recognition that immune compromised patients 10 are certainly very small numbers for each of these 11 special populations, immunocompromised patients 12 particularly solid organ transplant patients might be 13 a larger group such that they could be enrolled in the 14 trial but a point was made that it might also provide 15 an opportunity to assess pharmacokinetics in these 16 patients, address drug-drug interaction issues, how 17 one can dose the drug in hepatic, renal impairment, et 18 cetera. 19 It was emphasized that we need good 20 nonclinical data to support these studies including 21 extended duration studies. There was discussion 22 around biomarkers and imperfections of serologic</p>

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