



The Food and Drug Administration

Public Hearing on Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need

February 4, 2013
9:00 a.m. – 5:15 p.m.

FDA's White Oak Campus
10903 New Hampshire Avenue, Bldg. 31, Rm. 1503
Silver Spring, MD 20993

**Department of Health and Human Services
Food and Drug Administration**

**Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet
Medical Need Part 15 Public Hearing
February 4, 2013**

**FDA White Oak Campus 10903 New Hampshire Ave, Building 31, Room 1503 Silver
Spring, Maryland 20993**

AGENDA

Each speaker will have 10 minutes for their presentation. There will be 5 minutes following each presentation to offer an opportunity for the panel to ask clarifying questions.

February 4, 2013 Presentations

9:00 – 9:10 am Presiding Officer Opening Remarks

**Rachel Sherman, MD, MPH Associate Director for Medical Policy, Center for Drug
Evaluation and Research**

9:11 – 9:21 am (9:21– 9:26 am)

Jeffrey Spaeder, Quintiles

9:27 – 9:37am (9:37– 9:42 am)

Roger Echols, Infectious Disease Drug Development Consulting, LLC

9:43 – 9:53 am (9:53– 9:58 am)

Rebecca O'Connor, Parkinson's Action Network

9:59 – 10:09 am (10:09– 10:14 am)

Jeffrey Stein, Antibiotics Working Group (AWG), Trius Therapeutics

BREAK

10:14 – 10:30 am

10:31 – 10:41 am (10:41– 10:46 am)

Robert Guidos, Infectious Diseases Society of America (IDSA)

10:47 – 10:57 am (10:57– 11:02 am)

Paul Huckle, GlaxoSmithKline (GSK)

11:03 – 11:13 am (11:13– 11:18 am)

Jennifer A. Jackson, Cubist Pharmaceuticals, Inc.

11:19 – 11:29 am (11:29– 11:34 am)

**John F. Crowley, Amicus Therapeutics, Inc. John R. Kirk, Amicus Therapeutics, Inc. Jayne C.
Gershkowitz, Amicus Therapeutics, Inc.**

11:35 – 11:45 am (11:45– 11:50 am)

John H. Powers, *George Washington University School of Medicine, University of Maryland School of Medicine*

11:51 – 12:01 pm (12:01– 12:06 pm)

Nicole Mahoney, *The Pew Charitable Trusts*

LUNCH Ala Carte items will be available for purchase on site

12:07 am – 1:07 pm

1:08 – 1:18 pm (1:18– 1:23 pm)

David Ross, *George Washington University School of Medicine*

1:24 – 1:34 pm (1:34– 1:39 pm)

Andrew J. Emmett, *Biotechnology Industry Organization (BIO)*

1:40 – 1:50 pm (1:50– 1:55 pm)

Jonathan Sackner-Bernstein, *ExVivos, LLC*

1:56 – 2:06 pm (2:06– 2:11 pm)

Alan Solinger, *Pharmaceutical Product Development, LLC (PPD) Association of Clinical Research Organizations (ACRO)*

2:12 – 2:22 pm (2:22– 2:27 pm)

Roslyn Mannon, *American Society of Transplantation (AST), University of Alabama, Birmingham*

2:28 – 2:38 pm (2:38– 2:43 pm)

James I. Healy, *Soffinova Ventures, National Venture Capital Association (NVCA)*

BREAK

2:44 – 2:59 pm

3:00 – 3:10 pm (3:10– 3:15 pm)

Anthony Castaldo, *Hereditary Angioedema Association*

3:16 – 3:26 pm (3:26– 3:31 pm)

Jennifer Yttri, *National Research Center for Women & Families*

3:32 – 3:42 pm (3:42– 3:47 pm)

Brian Rosen, *Leukemia & Lymphoma Society* **Mark Velleca**, *Leukemia & Lymphoma Society*

3:48 – 3:58 pm (3:58– 4:03 pm)

Sally Okun, *PatientsLikeMe* **David Clifford**, *PatientsLikeMe*

4:04 – 4:14 pm (4:14– 4:19 pm)

Diane Helentjaris, *The American Medical Women's Association (AMWA)*

4:20 – 4:30 pm (4:30– 4:35 pm)

Randy Wheelock, *Consumer*

Open Public Comments

4:36 – 5:05 pm Closing remarks/Adjournment

5:05 – 5:15 pm

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
FOOD AND DRUG ADMINISTRATION DEPARTMENT OF HEALTH AND HUMAN
SERVICES

Public Hearing: February 4, 2013

**Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet
Medical Need; Public Hearing**

Panel Members

Presiding Officer: Rachel E. Sherman, M.D., M.P.H.

Associate Director for Medical Policy, Director, Office of Medical Policy Center for Drug
Evaluation and Research

Edward Cox, M.D., M.P.H.

Director, Office of Antimicrobial Products, Office of New Drugs Center for Drug Evaluation and
Research

Issam Zineh, Pharm.D. M.P.H., FCCP

Director, Office of Clinical Pharmacology, Office of Translational Sciences Center for Drug
Evaluation and Research

Diane Maloney, J.D.

Associate Director for Policy
Center for Biologics Evaluation and Research

Abigail E. Brandel

Attorney, Office of Chief Counsel Office of the Commissioner

Richard Klein

Director, Patient Liaison Programs, Office of Special Health Issues, Office of External Affairs
Office of the Commissioner

Proceedings

Welcome Remarks:

RACHEL SHERMAN:

Good morning to both attendees of the conference center and viewers via the live webcast. Welcome to the Part 15 Public Hearing Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need. I'm Rachel E. Sherman, Associate Director for Medical Policy, Center for Drug Evaluation and Research; I'll serve as the presiding officer for this hearing.

Before we begin I'll provide a few housekeeping announcements. To audience and panel alike, please turn off any mobile devices as they may interfere with equipment in the room. We ask that all attendees sign in; the meeting is scheduled from 9am until 5.15pm.

Restrooms are located in the lobby to the left and right hallways. We're planning a one 15 minute break during the morning session and one 15 minute break during the afternoon session. Today's lunch break is scheduled from 12.07 to 1.07 pm. There will be sandwiches, salads and beverages available for purchase in the lobby.

Before I continue my carefully scripted remarks, I was going to break up part 15 and make a few opening remarks. Today's topic is sufficiently nuance, sufficiently subtle, sufficiently broad and I think a few clarifying comments for the record may in fact be useful.

The question before us today is does the FDA need and can it use additional pathways, tools, options when considering approving a drug, and the rest of my friends and colleagues from biologics, anytime I say drugs I mean drugs from biologics and so I refer that thoroughly objectively and also in the spirit of friendship and public health service.

So where that is intended to be proof of a narrow population, typically a population of more serious manifestation of the disease often with none or few therapeutic options. And when I happen to talk on approving more narrow davits for safety mechanisms, which leaves residual uncertainty for the remainder of the population, either we don't know how it performs, we don't

know the risk factor ratios or we might even endorse it without sufficient evidence that it could be harmful.

There are disease areas in which we have done this for years with great deal of comfort.

Typically those are diseases for which there is a diagnostic and very clear capacity to withstand and we're very confident it will be used narrowly. HIV is an example; HPV is an example and there are a few other examples of that.

Decades and decades of history and experience has taught us that in other areas with antibacterial presence, often drugs are used very broadly and sometimes in populations in whom we're very uncomfortable not having data and then occasionally, more than occasionally, the approval may be delayed as we accumulate data in that broader population even though we now target a narrow population.

So turning to our law which is always very useful in thinking on what the FDA can and cannot, should and should not do, is to remind everyone, that we're out here to look at all test recently approved to show whether or not drugs safe for use on conditions prescribed or recommended, suggested in the labeling, based on substantial evidence. And substantial evidence is defined as evidence existing after controlled investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the written law. On the basis of which you can fairly and responsibly conclude by such efforts, that the drug will have the effect that it is recommended to have under the conditions for use prescribed recommended or suggested by the label.

So I think there are three points there worth reiterating; that the efficacy standard has served us well for over 50 years and is not what is under discussions today. What's under discussion today is applying that developing evidence. So first what does the trial look like? And we are out here, as part of our obligations in terms of promoting innovation and fostering development of novel innovative therapies in ensuring that trials are streamlined and efficient as possible.

The trial: the data itself has to be robust, it has to be accurate and it has to be interpreted by a qualified expert.

And then the third piece is the communication piece. We do that typically through labeling. But FDA as we all know does not regulate the practice of medicine, but we do influence it. And are we using all the tools available to us which could be helpful to us be they through statutes, be they through regulation, be they through guidance or be they through the authority we currently have to make sure that the community involved, should we approve the drug on a very narrow data set with a fair amount of certainty; so approved patients typically quite seriously ill but one might be more broadly.

Are we adequately informing and making sure the information goes to those who actually use the drugs or influence use of the drugs. So those who prescribe it; the physicians and other healthcare professionals, those who if you will, oversee the availability, formularies, pharmacists and other communities.

There have been two groups that have said yes we need to change the paradigm a little bit; one, Infectious Diseases Society of America last year, talked extensively and wrote extensively about a limited population model for antibacterial and during the PCAST report - president's council of advisors on science and technology in their 2012 report, also recommended a more limited pathway emphasizing labeling.

So today is part of the process of ensuring that we have a clear and transparent pathway and that we hear from all stakeholders involved so I very much appreciated the time and effort you have set aside in being with us today and I will now continue with my scripted remarks.

Turning to the speakers in the agenda: we have agenda speakers including 20 organizations or individuals.

The schedule presentation slot: in order to keep the agenda as close to the agenda as possible, I'll go over some ground rules.

First, this meeting is informal, the rules and evidence do not apply. No participant may interrupt the presentation of another participant. Only FDA panel members will be allowed to question a presenter.

FDA may recall presenter for additional questions at the end of the day assuming time allows and the presenter remains available. And mostly some of our most fruitful discussions have been here so if your schedule does allow, please try to stay.

Public hearings under part 15 are subject to FDA policy and procedures for electronic media coverage and FDA public administrative proceedings. Representatives of the electronic media may be permitted, subject to certain limitations, to video tape, film or otherwise record the FDA's public administrative proceedings including the presentations of speakers today. The meeting will be transcribed and copies of the transcripts may be ordered through the docket or accessed on our website approximately 30 days after the public hearing.

Each speaker has been given a 10 minute slot on the agenda, with 5 additional minutes for our FDA panel members to ask questions. If a speaker goes over the 10 minute slot, I'll start tapping the little red button with my pen and the time allowed for questions will be reduced accordingly. If the speakers end early, we intend to move on to the next speaker.

For those of you who did not register to speak or make a presentation but would like to present a comment, you may speak during the open public comment period at the conclusion of the hearing. Those interested in presenting during the open public comment period but have not already expressed interest should sign up at the speaker registration table in the front lobby by the end of the first break. Although we'll try and accommodate as many requests as possible, please remember that hearing is scheduled until 5.15pm and we'll end on time, I understand people have travel time.

However this hearing is not your last chance to comment. The docket will be open until March 1st and we strongly encourage all interested parties to comment so please see the conference registrar for details. Keeping up with the agenda we request that each speaker keeps to their allotted time so we are able to keep to our tight schedule. So before we continue, I'll like to turn to the panel to introduce themselves.

DIANE MALONEY: Good morning, I am Diane Maloney, Associate Director for Policy, Center for Biologics Evaluation and Research.

EDWARD COX: Good morning, Ed Cox Director, Office of Antimicrobial Products, Office of New Drugs Center for Drug Evaluation and Research.

ISSAM ZINEH: Good morning, Issam Zineh Director, Office of Clinical Pharmacology, Office of Translational Sciences Center for Drug Evaluation and Research

ABIGAIL BRANDEL: I'm Abby Brandel, I'm a lawyer at the attorneys office of Chief Counsel.

RICHARD KLEIN: Morning, I'm Richard Klein, Director of Patient Liaison Programs, Office of Special Health Issues, Office of External Affairs Office of the Commissioner

RACHEL SHERMAN: Thank you

We will now proceed with the presentations; and I apologize in advance I don't do well with names. The first speaker is Jeffrey Spaeder, Quintiles.

JEFFREY SPAEDER: Good morning. Dr. Sherman, thank you for you and your panel's opportunity to speak this morning. Some of the comments I'm going to talk about will guide you and pull out some operationalization of how a potential alternative pathway can be implemented.

My name is Jeff Spaeder, I am the chief medical and scientific officer at Quintiles. Prior to working in the industry I was a practicing academic cardiologist. Over the past ten years I have worked in a variety of settings both in academic, the bio-pharmaceutical industry, payer organizations both in clinical development as well as commercial roles.

This morning I represent my more than 27,000 colleagues who work at quintiles. For those not familiar with Quintiles, we are the global leader in biopharmaceutical services. Over the past six years, we have been involved in studies that have enrolled more than 8.5 million patients from around the world. And we have performed clinical research or participated in the commercialization 50 of the best-selling drugs and 20 of the large selling biologics.

At Quintiles, we understand the need to make new therapies available to patients quickly and also importantly safely. And as a result, we strongly support the adoption of the proposed pathway to speed the introduction of new therapies to patients with life-threatening illnesses and for those great with unmet medical needs. Our research suggests that patients are willing to use therapies approved under an accelerated pathway. This is based in part on a 2012 study in which we surveyed more than 5000 patients with chronic illnesses and found that these patients want access to medicines sooner, and those in greatest need are willing to accept more uncertainty about a therapy if it is the only potential to improve their health.

Some statistics from the survey I think are quite revealing:

- 71% of Patients in the United States surveyed with the following, quote: *"We take too long to make drugs available, which costs lives by forcing people to go without potential beneficial therapies."*
- 71% of patients also agreed that: *"Patients should be able to choose to take potentially risky medicines even it is not approved for use, if they feel it is their only chance to improve their health."*

However, we also recognize that new therapies that have been studied less extensively, such as those proposed in this pathway need to be used appropriately and only in settings where the clinical data are most compelling.

Quintiles's interest and support of the proposed pathway is based on two facts. First, we currently have capabilities, and secondly have implemented many of the components required for this clinical development paradigm.

We believe that not only is this proposed pathway is an important way to bring, new therapies to patients in need, but it is a feasible pathway that can be operationalized today.

Based upon our experience, we anticipate that there are six capabilities that are required to create a pathway based upon pre-registration studies, post-marketing evaluations with registries and observational studies and close monitoring of the post approved drug use.

The six capabilities are importantly inter connected. They must be adopted in an integrated approach to link preapproval findings and post-approval monitoring. Smaller studies in stratified

populations can be extremely powerful if the right questions are asked. However, the viability of the new pathway depends on integrating appropriate endpoints and other measures in the pre-registration trials to allow as you might say an "apples-to apples" comparisons with post-marketing monitoring and evaluation.

I'd like to now go through the six capabilities:

Capability 1: Incorporation of real-world data to ensure accurate powering and planning of studies. First, we need data-driven insights to plan and design pre-registration trials in stratified subpopulations so that these studies have a maximum likelihood of producing significant and scientifically valid findings. Failure to do so will leave the studies underpowered and ultimately delay decision-making about the value of the therapy. This insight requires sophisticated study designs based on real-world incidence rates. This type of insight currently exists now.

For example, Quintiles uses a tool called 'Infosario Design' that allows us to integrate real-world data including de-identified highly robust electronic data from more than eight million patient lives. We can combine this capability with an adaptive design studies to conduct smaller and more powerful trials. We can ask questions like "What is the potential of event rates in the specific sub-populations being studied" and other questions like "What types of sites are most likely to see the type of patients needed to be enrolled in these studies?"

With these answers, we can form simulations of potential traditional and adaptive trial designs in real time to design and make informative our decisions about how we conduct and design these studies.

Capability 2. Precise identification of the patient subpopulation:

The accelerated pathway will depend on precise identification of study populations and subpopulations. We are now using genomics, RNA sequencing expression analysis, soluble and tissue-based biomarkers, and advanced statistical methodologies to identify the appropriate subpopulations. With these technologies, we can identify the exact patients that are most likely to benefit from a drug and to be included into a study and to maximize the benefit-risk profile of the drug.

Capability 3. Incorporation of surrogate endpoints that anticipate the needs of post-marketing monitoring and evaluation. Pre-approval trials must anticipate the research questions that will be

needed to be evaluated in a post approval setting. Trials must incorporate surrogate endpoints, biomarkers and patient reported outcomes in order to facilitate research after the drug has been approved. This will require a new way of working that breaks down existing operational silos between clinical studies and those that perform post-marketing research. Epidemiologists and other observational research experts will need to participate in the design of pre-registration studies to operationalize this integration to ensure Like-to-Like comparisons between pre- and post-registration studies.

Capability 4. Establishment of higher “quality sites to limit variability:

Smaller studies in stratified subpopulations intensify the need for research precision that exceeds currently accepted levels. The accelerated pathway will require a higher-quality study site and investigators than are currently required for traditional studies. This necessitates collaborations with investigators and the use of sites that exceed existing quality and operational metrics. These specialized sites are increasingly being used in clinical research. And as an example, Quintiles' use of the Prime and Partner Sites program identifies and partners with sites and investigators who are capable of delivering these enhanced research capabilities.

Capability 5. Implementation of registries and post-approval observational studies:

Registries can be used to evaluate the efficacy and safety of a new therapy in the narrowly defined subpopulation in routine clinical practice for which the safety and efficacy have been demonstrated in pre-registration studies. Conversely, observational studies can be used to assess the real-world efficacy of the drug in all patient populations, even those not specifically evaluated in pre-registration studies.

Regarding Question 6 that the panel asked for comment, we believe that there is value in incorporating provisions to formal pathway designation or logos to reinforce that the drug is to be used only in a specific subpopulation. Registries offer additional constraints to ensure drug use only in an approved indication and in populations and can therefore be discouraged for off label use. We already know for instance, that registry participation has already been used to limit the use of certain therapies, both therapies and medical devices.

In our experience, well-constructed registries and scientifically rigorous observational studies augments insights gained from pre-registration studies. This provides knowledge about the

benefit-risk profile of a drug in the real-world which is frankly the most important piece of information the practicing healthcare providers and patients care about the most.

The sixth and final capability is the ability to monitor drug use in patients not participating in the registries or observational studies.

Prospective surveys based on electronic health records can be conducted to monitor drug use in patients who are not enrolled in registries or an observational study. This would provide insight into the real-world use of the therapy and help us answer three questions:

First, the percentage of patients or prescriptions that are using the drug consistent with its labeled indication; secondly, the ways in which patients who utilize a drug off-label differ from those previously studied population and third the outcomes of these patients.

In conclusion, all the necessary pieces are in place to implement an alternative pathway. The tools and data required to effectively implement a pathway exist now. An integrated approach to the continuum of development and real world prescribing can be constructed with current capabilities.

This brings me to my final thought on how the panel and agency may wish to proceed. To borrow a phrase common in the technology world, we must "think big, start small, and scale fast". This will allow us to make the alternative pathway a reality so that patients can benefit without delay. With the right therapies and the right indications, we can start today. Thank you

RACHEL SHERMAN: Thank you for our comments, questions from the panel? Ed Cox?

EDWARD COX: Hi, thanks for your comments. I was wondering if you could talk a little bit more on your tool, the Infosario Design. You discussed the endpoints, and thinking about post approval, I'm wondering about the type of information you can get the Infosario Design tool to try and help with clinical trials; does it get to the type of issues and data information that help in planning a clinical trial or is it more for post approval?

JEFFREY SPAEDER: It can be used really for both but we typically use it for pre-approval study design. So right now we have more than eight million unique patient lives in the tool with very robust endpoints, comorbidities, concomitant medications coded in standardized syntax into the

database. And so if we want to ask for instance, what type of diabetes population might be eligible for a study or importantly what the event rate would be, we can plan that ahead of time. And that is critical especially for certain types of smaller sub-populations of studies, where you really need to identify the event rate and what that event rate is in that particular patient population. So you can kind of tweak the inclusion, exclusion and find what the event rate is, or the potential enrollment rate would be.

ISSAM ZINEH: It seems this 6 point paradigm been taken out from quintiles and applied to the broader drug enrollment context, would you say, that all of these are equally well developed? It seems to me as though post approval monitoring or surveillance piece might be for example a bit niche, relative to some of the others.

JEFFREY SPAEDER: certainly the first five capabilities currently being used, implemented and we use them on a regular basis. The sixth one about looking at off label use, those capabilities exist now and we could utilize them. But there hasn't been a setting to really utilize and operationalize those capabilities. But using things like Infosario Design or some other capabilities that we have, we could get at that number 6 in a very very, almost immediately but there hasn't been a lot of use for it quite yet.

RACHEL SHERMAN: any other question from the panel? I will just encourage you to submit to the docket not only your 2012 report, but this tool and any that you have on the post marketing question, because we as an agency are struggling mildly, and very successful, but struggling mildly to develop something, looking at safety data for post marketing. So we'll be very interested on any thoughts you might have on how to expand that, you think it's factually and fairly straight forward?

JEFFREY SPAEDER: we would be happy to, thank you.

RACHEL SHERMAN: Thank you. Our next speaker is Roger Echols from the infectious Disease Drug Development Consulting

ROGER ECHOLS: Thank you Dr. Sherman, I appreciate the opportunity to address the committee on this important subject. My name is Roger Echols, I'm an infectious disease trained physician

and currently working full time as a consultant supporting sponsors and investors in the area of anti-microbial therapeutics.

As an infectious disease physician who completed his training in the late 1970's, I was a beneficiary of previous research and development efforts that provided a broad range of therapeutic agents with which to treat my patients.

The practice of infectious disease was largely consultative and focused on microbiologic diagnosis. Once a correct diagnosis was established; it was unusual not to have a drug with the appropriate spectrum of activity. My experience in drug development include 10 years as an investigator designing and conducting clinical research trials mostly involving extended spectrum cephalosporin and later fluoroquinolones

It was my interest in Atlanta that led me to the pharmaceutical industry where for 19 years I led clinical development teams for anti-bacterial, anti-viral and anti-fungal programs. I've continued my focus on anti-microbial therapies as a consultant for the past 5 years.

The viewpoints I express today are solely my own and not coordinated with any current or past client.

So first question; is a new pathway necessary to address the growing challenge of multi drug resistant bacteria? At first glance I believe the answer is no. I base this on the successful use of the accelerated approval regulation which dates back to 1992 and was most recently applied in December of last year for the approval of bedaquiline for the treatment of MDR tuberculosis.

It's important to understand that the accelerated approval process calls for the use of a surrogate marker, which is defined as a substitute for clinically meaningful endpoints that is a direct measure of how patient feels, functions or survives.

However, despite my opinion on the new regulatory or statutory rules are not essential, I would encourage any effort to clarify and facilitate a focused approval mechanism targeting multidrug resisting bacterial pathogens.

Let's look at the bedaquiline story. This diarylquinoline provided a new mechanism of anti-micro bacterial activity. It was studied in two small prospective controlled clinical trials, and it was in patients with pulmonary tuberculosis caused by resistant strains. Importantly the primary

surrogate endpoint was sputum conversion, which means that eradicating or eliminating the TB pathogens from the patients sputum.

In study one, a hundred and sixty patients were randomized, the treatment difference observed at 24 weeks was 20% which was statistically significant. In study two which was really the first study conducted, 48% of the bedaquiline treated subjects had sputum conversion at 8 weeks compared to 9% for controls; again highly significant.

The safety data set of 335 patients included an ongoing open label study; there was an imbalance in mortality identified in the larger clinical trials. However attribution to study drug could not be determined. The published label reads: reserve sirturo for use when effective treatment regimen cannot be otherwise provided. Sirturo is not indicated for the treatment of latent, extra pulmonary or drugs sensitive to tuberculosis. In addition there's a black box warning for the increased risk of death and the identification of the potential for sirturo to cause prolongation of QT interval.

As for the post approval commitments, the company was required to conduct a confirmatory prospective trial of clinical endpoints and actively collect safety data through patient registry. All promotional materials are to be pre-reviewed by the FDA even after the usual 120 day introductory or launch period. I view the bedaquiline approval within the limitation of accelerated approval regulations as highly successful mainly because it was targeted development for an MDR pathogen and it used surrogates of microbiological eradication to access clinical benefit.

For me the key issue for advancing promising treatments for MDR pathogens is not the number of patients or type of studies but rather, what are the acceptable endpoints for accessing clinical benefits? It's remarkable to me, that the current FDA definition of clinically meaningful benefits, namely: the direct measure of how a patient feels, functions or survives, actually stems from a definition of accelerated approval regulation, and its definition of a surrogate marker.

Unfortunately, mortality, although objective, is highly confounded endpoint in patients with MDR pathogens, especially gram –negative organisms. These infections are usually nosocomial which by definition means, the patients are admitted to the hospital for other reasons. Patient function or symptoms are also highly confounded in acute care settings. Treating physicians

understand that the purpose of antimicrobial therapy is to either kill or inhibit growth of the offending bacteria and that failure to do so results in clinical failure.

In day to day practice, physicians look to drugs to eradicate the bug, plain and simple. These results are informative to physicians. The story behind the development approval of vancomycin may be considered ancient history but it serves as a model for the discussion today. Developed in the 1950s, it was selected specifically for its activity against penicillin resistant *Staphylococcus aureus*. This was long before MRSA came on the scene. Because its approval predated the Kefauver-Harris amendment, a demonstration of efficacy was not required.

Vancomycin efficacy was reviewed and supported in the 1960s under the DESI program, what was compelling evidence. It was mostly a series of anecdotal cases of *Staphylococcus aureus* bacteremia often endocarditis in patients who had failed prior antimicrobial therapy. Clinical outcomes were defined in terms of what we would call surrogates now namely, vital signs and microbiological proof of the elimination of the organism.

So is a new pathway going to improve on existing accelerated approval regulations? Identifying specific MDR pathogens such as pseudomonas, acinetobacter, KPCs and ESBL producing organisms will provide transparency to the investment community.

Limiting expectations for return on investment is equally important. LPAD is a good start however this tiered approach does not address the identification of acceptable clinical endpoints. If we continue to try to fit life threatening diseases into the field, functions or survives paradigm, we will not reduce the regulatory risk or uncertainty which weighs against investment today. We need to accept alternative clinical endpoints that are measurable and logical and valid using contemporaneous data.

Even named patient or emergency use protocols could provide meaningful information. Prior to the approval of the IV formulation of ciprofloxacin in 1990, they are provided express air shipment of drug to site anyway in North America for the treatment of seriously ill patients not responding to available therapy. Close to 2000 patients, mostly with pseudomonas infection being treated in ICUs received the drug. What this compassionate use program was not designed to collect efficacy data, it could have done so, although not in a monitored GCP way.

The agency in convening this meeting has expressed concern about drugs or biologics approved under this new pathway. With regard specifically to MDR net gram negative pathogens, I think this is not a problem. Drugs developed for limited population will have expectations of limited use. This will be reflected in the cost of these new drugs, which has been estimated at \$5,000 per treatment course. Antibiotic stewardship will restrict use to specific patients and third party payers will reinforce restricted use by their reimbursement process. Even if these drugs are used or allowed for empiric use, this decision can be reassessed frequently based on real time patient specific evidence.

In conclusion, the existing statutory rules for accelerated approval permits pathogen targeted conditional approval based on microbiologic surrogate endpoint.

If additional legislation could help, fine, but new regulations should not re-create new barriers or new regulatory uncertainties. Most critical is to identify the target pathogen and the target patient population and within those parameters, we need to define acceptable microbiologic endpoint to serve as valid evidence of clinical benefit. The cost of these new therapies for these limited populations will ensure appropriate use. Thank you very much.

RACHEL SHERMAN: thank you, questions from the panel? Doctor Cox?

EDWARD COX: Hi Roger thanks for your comments. One question on that, the pathogen focused issue. Just thinking about, wondering if you want to comment on this. Patients will have infections in a variety of different tissue sites. As one of the challenges we face here, how to, in essence, look at data from across different body sites. Take for example; I will throw this out say urine, lung, blood stream, intra-abdominal something like that. Any thoughts on clinical trial design and how to grapple with the challenge of looking at different body sites?

ROGER ECHOLS: certainly different pathogens at different body sites can have different clinical impact and although any, body site can spill over systemically; a patient can get septic and die. So, it's still to me about the bug and can you eradicate the bug. And I think you can define not only a targeted pathogen population, but also targeted patient population in terms of where the infection is.

So dealing with bacteremia patients to me would be one of the best populations to look at. Although again, it's a sub-set of a sub-set and how you incorporate those patients into clinical trials i think, has to find new ways. Our current method of setting up clinical trial sites hoping that a particular organism in the bloodstream comes along is not going to work but there are ways I think, again with either contemporaneous historical data, using prospective data collection as a comparison, and open label studies but also even a kind of, I think the compassionate use program I ran with Cipro.

We can deliver drug in eight to ten hours in North America, so when a patient is failing therapy, they act of their own control. And if you implement a new, introduce a new therapy and you can particularly, if you can identify eradication of the organism, I think that goes a long way to improving the efficacy of the drug.

RACHEL SHERMAN: other questions? Thanks for your presentation.

DIANE MALONEY: I just had a question on the concern about off label use and you talked about stewardship and I think the proposals you put on the table don't have a role for FDA. Curious about what FDA's role if any might be?

ROGER ECHOLS: well I think it starts with the label and I think it is followed up by things that Jeffery was mentioning earlier about post approval monitoring and whether it is a patient registry or looking at databases. But I think the databases will be available given the electronic age, computer records we have. Particularly through the payers that might be paying for this. When I'm thinking of a targeted population, with resistant pseudomonas or resistant acinetobacter, infections, A they are not that common today but they are growing so we are trying to develop drugs for the future but at the same time, if we have the drugs available, we should I think, anticipate again that usage might grow but it can be monitored.

I truly am not a commercial person but I know price pressures in the antibiotic world and if you are charging a lot, people are going to be watching that every step of the way.

RACHEL SHERMAN: other questions? I have two. Who would be responsible for stewardship? Do you have any thoughts about that?

ROGER ECHOLS: stewardship is something we did thirty years ago. In Albany, we introduced an antibiotic order sheet in the early 1980s. It told us what physician was using what antibiotic for what reason and published data on this. It worked very effectively. Stewardship has gotten much broader than that but it is basically any hospital that has an infectious disease, physician or people with interest in how antibiotics are used, have antibiotic stewardship programs now and they take various forms and they are evolving but its common vernacular today.

RACHEL SHERMAN: And few functions survive, do you have a suggestion on how we might expand on that?

ROGER ECHOLS: not to be too direct but I think I spoke with Bob Temple about where he came up with this idea and he says that is what everybody was talking about but really never validated in terms of acute infectious diseases. It may fit perfectly for chronic diseases and other things but it doesn't fit for acute infectious diseases. So, I find it really a barrier for evaluating treatment benefit of antimicrobials.

RACHEL SHERMAN: thanks for your comments. We encourage you to put the full text in the docket. Our next speaker is Rebecca O'Connor from the *Parkinson's Action Network*

REBECCA O'CONNOR: Good morning Dr. Sherman and others, thank you for the opportunity to comment today. My name is Rebecca O'Connor, and I am director of government relations for the *Parkinson's Action Network*; the unified voice of the Parkinson's community on public policy issues. We represent collectively the Michael J Fox foundation for Parkinson's research, the American Parkinson's disease Association, the Davis Phinney foundation, the national Parkinson's foundation and the Parkinson's center alliance.

And in full disclosure, I wore the ravens purple completely by accident and I am a disgruntled 49ers fan at home. But congratulations!

Parkinson's as you may know is a chronic progressive neurological disease which affects an estimated 500,000 to 1.5 million Americans and there is currently no buyer marker for Parkinson's or a treatment that slows or stops the progression of this debilitating disease. The treatments that do exist are based on a 40 year old treatment s which treats only some of the symptoms of the disease and eventually you lose effectiveness.

So, for obvious reasons, PAN strongly supports efforts to develop new treatments that will enable people with chronic conditions like Parkinson's to live stronger, healthier lives particularly those with unmet medical needs.

We also support the commitment and flexibility and expedited approvals of this proposal promises. With that said, we believe that the benefits of the accelerated approval pathway proposal, will depend on the implementation and details which we hope will be forthcoming. Specifically, we are concerned that without additional guidance from the agency, a limited use approval pathway may restrict patient access to new therapies.

Diseases like Parkinson's affect each individual differently. There is no one size fits all medication. For that reason, physicians often experiment with different types of medications or combinations of medication before they find a combination that fits and addresses the individual's needs. Occasionally of course, this means prescribing off label. And while we certainly don't think the FDA should condone or encourage rampant off label usage, it is important for people with Parkinson's and other chronic conditions that doctors have, within reason, the ability to continue to prescribe off label.

We also note that it might be an incentive for corporations, certainly to use shorter approval pathways with smaller, cheaper clinical trials. Again, another boom to us on the one hand, because of course clinical trials being as expensive and onerous as they are, they are a significant hurdle for a population. But at the same time, we need to balance pathways that expedite approval but that might limit and constrict off label use. There is a balanced process there and we urge the agency to provide additional guidance as to how this will work in implementation.

We also flag that this might cause significant insurance challenges for patients. Specifically, we are concerned that providers, private payers and Medicare, may foul reimbursement for off label use of drug approved to limited use pathway. We again, urge that you create some additional guidance about that specific issue.

And finally, we also want to flag that while we are encouraged that the guidance indicates that certain drugs will eventually, if there is demonstrated clear evidence to support it, be approved

for broader population, the guidance does not go far enough in our view in spelling out what that additional data is and what is necessary to approve it for a broader population.

A final note, and it has been touched on already, the guidance also, it would be helpful to know a little bit more how the agency plans to define sub-populations of disease for so many chronic conditions. There is no clear defined sub-population.

So I thank you, on behalf of PAN and the Parkinson's community, very much that your efforts, ensure patients have access to new treatments but urge you to continue to flesh this proposal out and we will be submitting detail comments on that record.

RACHEL SHERMAN: Thank you for your comments.

DIANE MALONEY: just a question on your last point about sub-populations of diseases. I recognize it is a challenge in the Parkinson's area. Do you have thoughts on whether it's now or for the docket? I would be interested in knowing.

REBECCA O'CONNOR: Thoughts on how you would, how we would, ask you to give clear guidance on how to sub define subpopulations? Yes I think we're definitely going to address that in our comments. I would say it's a significant challenge across the board not just for Parkinson's, so I don't have it to offer right now. I will certainly give thought to it. It's a great question.

RACHEL SHERMAN: further questions?

ISSAM ZINEH: so we just published a draft guidance on enrichment strategies in drug development that deals with the question of subpopulation medicine in large respects. And one of the key questions in that guidance is how much data you need in the other population to get some assurances of safety for example or maybe get some whiff of drug activity. So as you were talking, I am thinking about what sounds like to me, that the Parkinson's community, is really one that if a drug were to become available on a limited use path, through limited use mechanism, that there would be significant interest in trying new therapies on an individual level, meaning off label use or quite a bit off label use.

So from a willingness to accept uncertainty or risk standpoint, can you comment a little bit on just your opinion on the Parkinson's community in terms of how much willingness the community, how much uncertainty especially on the safety side, the community is willing to accept for novel therapies.

REBECCA O'CONNOR: sure. It's a great point. If you have a rare condition, such as a subpopulation of the disease as devastating as I said as Parkinson's, your risk-benefit profile is completely skewed to the normal population. You are more willing to accept significant risk, which is going to be the difference between getting treatment or not for yourself and the future generations. So I think it's a great point that folks with Parkinson's and particularly, it depends on how this plays out, would be willing to accept heightened risk in order to get these treatments.

RACHEL SHERMAN: other questions?

Just to remind you when you think about your comments for the docket, they are not an agency proposal before you but rather there are two proposals out there, PCAST and IDSA but we are here seeking your thoughts about what a proposal might look like to come from an agency.

Thank you for your comments.

RACHEL SHERMAN: our next speaker is Jeffrey Stein, Antibiotics Working Group (AWG), Trius Therapeutics.

JEFFREY STEIN: Thank you Dr. Sherman and the rest of the panel for the opportunity to present. My name is Jeff Stein and I am here representing the antibiotics working group. I am also President and CEO of Trias therapeutics. So the antibiotics working group is a non-profit organization. We are essentially a coalition of companies that are focused on the development of new antibiotics. And we have a strong commitment to dialogue with the FDA's office of antimicrobial products and other divisions as well.

You might ask why these competitors would get together and in fact we share a common objective and that is to improve the regulatory, investment and commercial environment for emerging antibiotic companies in order to expedite the development of antibiotic drugs. So, we

are very pleased with the FDA's initiative to come up with an alternative to development pathway.

And we support this. However, we would urge the FDA to consider the potential expansion of this alternative development pathway to drugs that could be already approved in broader populations. This is theme you will see in today's presentation.

Some of the important considerations for antibacterial drugs is that the definition of an unmet medical need should include future needs not just the needs we see today. This is consistent with the recently passed GAIN act. Many significant unmet needs do not presently have a feasible path for a label. And, we see the alternative development pathway as an opportunity to address this issue.

Finally, because the standard for the approval of antibacterial drugs is non-inferiority, we believe that safety should be an important consideration in this pathway.

So as it is written in the federal register, and contemplated in the LPAD proposal, the alternative development pathway really focused on something that looks like this.

Probably, a new class of drugs, limited preclinical and safety data, with potential emerging indications such as acinetobacter, NDM-1, or ESBL infections and typically this could be a new chemical class. However for these types of infections, we might have drugs that are being approved in broader indications. Because there is no alternative approval pathway at present, all such drugs that could be addressing these important infections are currently getting a label for a broader infection.

These are typically improved class antibiotics that could be glycol peptide, macrolides, oxazolidinones etc. And they are seeking initial broad approval in skin infections, lung infections and UTI for example. An example here is a drug called linezolid which first had an approval in enterococcus infections of this is a pathogen specific approach and later, achieved a broader label. On the left however, many of these improved classes of drugs are seeking a broader label initially and may have an opportunity to obtain a narrow indication in one of these emerging infections.

We would urge the FDA to consider that an alternative approval pathway should consider both. However if a sponsor has a broader label , it would be a challenge to accept any restrictive labeling or burdensome monitoring that could be associated with the alternative approval pathway and this is a theme you will see as we address the question.

So with respect to effectiveness of adding an additional pathway we believe that it could be highly effective because currently available pathways do not adequately address the burden of the operational and financial feasibility of current registrational studies.

As I mentioned in the prior slide, the alternative pathway should provide regulatory standards for diseases not addressed by the current regulatory framework. I mentioned linezolid previously, about 50% of the use of that drug is off label and this could be contributing to the emerging resistance we have seen. As an example, it is not indicated for prosthetic bone and joint infections osteomyelitis or bacteremia yet a substantial amount of its uses is in those indications. Certainly it would be optimal if there were a feasible pathway to get labels for such indications.

And finally, alternative pathways should incorporate animal efficacy NPD key modeling data as important elements in establishing efficacy.

Question two which serious or life threatening conditions could benefit? Certainly, multi-drug resistant pathogens; rare pathogens are mentioned on the prior slides. When there is potential safety concern for example, when patients who are really impaired have a limited repertoire of antibiotics, that could be efficacious. And finally unmet needs that fall outside of traditional labeled indications.

Question three, measures to ensure appropriate use: we believe that a pathway as mentioned previously should apply different considerations for drugs that already have a broader label. A feasible path for a limited label would minimize off label use.

Third, we believe that appropriate stewardship should be incentivized as one mechanism for providing an incentive perhaps provide additional extension of data exclusivity for each year that a company embarks upon a stewardship program.

And then finally, with respect to preventing the emergence of further antimicrobial resistance, certainly pricing and reimbursement is one way to do so. This is not under the purview of FDA however incentivizing antibiotic development is an effective measure to ensure new drugs will be available to combat emergence of resistance.

So, any mechanism that is put in place to encourage the development of novel antibiotics will certainly help with the development and emergence of resistance.

Question four, would a pathway help address current challenges?

Yes, with caveats. We believe that the pathway will help with the development of drugs for the pathogens or for the diseases indicated here. However this assumes development cost will be reduced and or reimbursement will be enhanced, commensurate with reductions in the patient population for these narrow indications.

Question five, appropriate risk-benefit for limited populations: there are a number of considerations that we believe should be taken into account. I won't be going through each of these but they are there for the written record.

And the last bullet point, these considerations should influence the extent of efficacy and safety data required for approval in any post approval monitoring requirements.

What this means is the more data you have, the less burdensome restrictions should be.

Finally formal designation or logo: Again we believe that different considerations should be applied for a new therapy that has limited safety versus a therapy that already is approved for a broader label. And finally hospital settings; we have to remember that neither physicians nor patients have an opportunity to see the label, so it is only visible to the clinical pharmacist and therefore special label may have limited utility in this type of setting.

And just to conclude, we applaud the FDA's commitment to explore this new pathway. We believe that explicit rulemaking or guidance for antimicrobial is desperately needed and then finally we would urge the division, the FDA, to consider pathogen focused development.

Certainly this was mentioned earlier, we think this is an interesting approach and should be taken under consideration.

Thank you.

RACHEL SHERMAN: thank you for your comments. Questions from the panel?

DIANE MALONEY: thank you, I have one question on one of your slides. You talked about measures to ensure appropriate use in a limited label would minimize off label use. I am curious to know about that compared to what is happening now where we have what you might call limited labeling?

JEFFREY STEIN: So I was referring to indications such as osteomyelitis or prosthetic bone and joint infection. There is no visible pathway to obtain a label in such indications. If there were a feasible pathway, certainly clinicians would prefer to use a drug that has that label.

RACHEL SHERMAN: Just following up on that, because I was also a little confused from your broad scenario, so if the topic of the meeting is in a sense how accelerated availability in a non-burdensome way, if there is a broad indication out there, how does narrowing it help achieve that goal? And how does, since you talked about perhaps the off label use contributing to the resistance, if a company were then to in a labeled indication, how does that help prevent development resistance if it is to be used in the same setting?

JEFFERY STEIN: the intent of that slide was to indicate that we should not impose a burden of narrowing of a label or induce burdensome monitoring for a drug that already has a broad label. For example, if you have a drug that is labeled for skin indications, yet you know that it could be effective against MDM-1, one you would not want to discourage a sponsor from exploring an addition label for MDM1 by adding on any burdensome monitoring requirements.

EDWARD COX: thanks for your comments. I was just curious, one of the issues I am wondering we are dealing with here seems like we are, is the issue of infrequently occurring conditions or infrequently occurring conditions due to particular pathogens of interest and you touched on that somewhat. Any thoughts on that? We've heard some of the other speakers about potential

approaches. Thoughts you might have about how to tackle the issue of infrequently occurring additions, conditions or pathogens of cause?

JEFFREY STEIN: This is a challenging area to develop a drug for an infrequent infection, acinetobacter for example, a rare pathogen for example; we believe the animal rule is one where we might be able to tackle this issue. If you demonstrate in an animal model infections which we all know is highly predictive of efficacy in humans, and have a database, a robust safety database and this is one pathway towards these rare pathogens.

EDWARD COX: just another question you touch on the issue of stewardship. Wondering if you can comment for a minute on the tension between stewardship and economic returns on development of new antibacterial drugs, any thoughts you would have to share on that?

JEFFREY STEIN: Yes. We think it is important to have an appropriate stewardship. However, this is a financial burden to a company which is why one of the potential mechanisms to facilitate that would be to provide additional data exclusively for any company that involves, embarks on a stewardship program.

RACHEL SHERMAN: Is the implication that you believe stewardship should be in the hands of the company?

JEFFREY STEIN: We think it should be in the hands of not only the company, but also the institution as well and encouraged by the FDA.

RACHEL SHERMAN: Other questions? Since we are ahead of time, I thank you all. I do have a question for anyone on the panel. You all touched a little bit or many of touched on, several views, the issue of power. What does power mean, with a very, very limited population of 20 or 30 or 50 or 100? Does anyone want to try and tackle that one?

JEFFREY SPAEDER: I think you get to one of the points about the challenges with working with subpopulations. I think it gets to questions about reducing variability. Identifying the event rate very accurately above, I think it also gives the point about including endpoints; patient reported

outcomes among biomarkers, even if they do not become companion diagnostics, and other metrics that can be measured both in the preapproval and in a post approval setting.

Because you are right, you need to get as much data available to look across pre and post approval because that is going to be an issue. By definition, with a smaller population, you are not going to have the large P values components that you might have with the traditional study. But including other endpoints and portal endpoints that can be measured post approval, are important. I think that addresses the issue.

ROGER ECHOLS: I am a firm believer in statistical power and evidence based medicine to me is the big issue, though question is what your endpoint is? If you are looking at a clinical endpoint it is not very sensitive to drug effect, where the look at a microbiologic endpoint is, it is much more sensitive to drug effect. And for instance, 100 patients with staphylococcal bacteremia that if you compare in a randomized fashion, but if you look at a time to eradication of the organism, you could show superiority in 100 patients to reduce the time of bacteremia by 50%.

Now that is not an acceptable clinical endpoint in today's paradigm. Because ultimately, patients may survive or they may ultimately all get better, although some will get better faster and even though we have used time to resolution for other indications, so it is not out of the realm of possibility. But it is really based on microbiologic endpoint and that's much more sensitive. And you can look at double tubular type media studies, you can look at all sorts of examples where microbiologic endpoint, because they are more sensitive to drug effect, create a very solid statistical evidence if you accept microbiologic endpoint.

RACHEL SHERMAN: Thank you, go ahead.

JEFFERY STEIN: with respect to power, one might consider a concept of conditional approval based on an initial broader non inferiority margin or less robust powering assumptions. Provide the sponsor an opportunity to get an initial conditional approval in exchange for a commitment to continue that trial under a more stringent powering or non-inferiority requirement.

RACHEL SHERMAN: just point of clarification, when you say conditional approval are you referring to subpart H accelerated approval or something else?

JEFFREY STEIN: Something else that does not exist yet.

Rachel Sherman: Thank you, that helps. Any other questions for anyone of the panel? Okay we are doing great. We are four minutes ahead of schedule, so we will add that to your break. Please be back at 10.30

RACHEL SHERMAN: welcome back, our next speaker is Robert Guidos, from the *Infectious Diseases Society of America (IDSA)*

ROBERT GUIDOS: On behalf of the Infectious Diseases Society of America, I'd like to thank the FDA for holding this very important meeting. IDSA strongly supports the creation of limited population antibacterial drug approval pathways. LPAD will provide an essential mechanism for bringing urgently needed new antibacterial to market.

As the number of patients coming to antibacterial resistant infections continues to rise, the number of new antibiotics and developments have plummeted. Over the past few decades, we have witnessed company after company withdrawing from this critical area of medicine while the death toll climbs. Now there are a handful of large and perhaps two dozen small companies still engaged in the antibiotics R&D enterprise and there are persistent rumors that additional companies could withdraw. This is unacceptable. To lose another company or additional set of experts in this area would be a disaster for the United States. We must act to address this crisis.

In addition to creating new economic incentives such as the exclusivity incentive congress enacted last year, we urgently need feasible FDA approval pathways that advance development of critically needed antibiotics.

The uncertain US regulatory environment is the primary reason that the few remaining pharmaceutical companies still invest in antibiotics R&D before they plan to focus future efforts outside the United States.

FDA has an essential role to play in ensuring that Americans have access to safe and effective drugs, but in so doing the agency must ensure that the risk associated with approving new

products are properly balanced with the need to provide patients in desperate need, the access to beneficial products.

Today when it comes to antibiotic and particularly antibiotics needed to treat patients with the most serious bacterial infections, FDA's benefit-risk equation has been out of balance.

IDSA believes the LPAD approval mechanism is a game changer that will rebalance the benefit risk equation and save lives. LPAD will provide an important new approval pathway option for companies interested in and able to develop antibacterial drugs that treat the most serious infections. At least fourteen companies and twenty four medical and public health organizations including the American medical association have lined up with IDSA in support of the LPAD's creation.

Why do we need LPAD?

It is not feasible for the antibacterial drugs to treat serious infections due to the highly resistance bacterial pathogens, to be developed using traditional large scale clinical trials due to the limit number of patients in which such serious infections occur. Instead, under the LPAD mechanism, a drug's safety and effectiveness will be studied in substantially smaller and more rapid and less expensive clinical trials much like the Orphan Drug Program premeds for other rare diseases.

LPAD products then would be narrowly indicated to be marketed to and used in small well defined populations of patients, to whom the drug benefits have been shown to far outweigh the risks. Many bacterial diseases have a broad spectrum of severity. The LPAD mechanism is intended to address the needs of the special population of patients with serious manifestations of such diseases who lack satisfactory treatment. In caring for such severely ill patients with limited treatment options, the patient healthcare providers, regulators and society can tolerate a greater degree of uncertainty about overall risk associated with the drug than can be tolerated in patients with milder manifestations of the disease or those who have more satisfactory treatment options.

The LPAD mechanism should not be used to approve antibacterial products that treat less serious infections or infections where sufficient alternative therapeutic options exist.

As IDSA envisions this pathway, if a company chooses to seek an LPAD designation for its antibiotic and FDA approves the designation, and ultimately approves the drug, then the drug's

label will include the special designation; a description of the indicated population, the rationale for eliminating the indication and the special LPAD logo.

Through this high profile new label, FDA will provide notice to the healthcare community, providers, payers and patients that these products carry greater uncertainty, that is less precise estimates of risks and as a result the drug marketing and use will be limited to the indicated population. An added benefit, LPAD's products limited marketing and use will help slow the rate at which resistance to these drugs develop; an important goal for the medical, public and patient communities.

A critical importance, the LPAD mechanism must ensure that clinical decisions making, remain in physicians hands. FDA will have an important role to play in ensuring that appropriate conditions of use are described in the drugs labeling but should not have a role in authorizing or prohibiting use of approved products within the practice of medicine.

However FDA should monitor LPAD products safe use through its existing census system and other mechanisms.

So why would companies pursue a product that would have more limited use?

Currently antibiotics are typically priced far below their true value to society. As with open drug designations and LPAD designations, it is expected to increase the price of these drugs remarkably compared with traditionally approved antibiotics.

Making investments in LPAD antibiotics will be more attractive to pharmaceutical companies. The drugs higher price will in turn encourage payers to help their communities and providers to play a more active role in ensuring that LPAD's are used as narrowly as indicated which will also help preserve the drug's effectiveness over time.

Pricing LPAD drugs at a premium is easily justified based on the severity of the target disease, the limited availability of alternative therapies and by granting the patient potentially decades more quality life due to the effective therapy.

And in addition because multi drug resistant infections are more expensive to take care of than susceptible infections, LPAD's premium cost will be offset by reducing the excess healthcare cost due to resistance.

I want to address two misconceptions that I recently read in the various media reports about LPAD.

First over the past year I'm pleased to say I've heard nothing in my discussions with FDA officials that would signal the agency had any interest or plan to take action to penalize physicians who might prescribe LPAD drugs off label or to otherwise implement restrictions on off label use. From the IDSA position, this would not be supportable. It is our expectation that the FDA will continue to stay on this course.

It is a fact that the vast majority of inappropriate antibiotic use that has occurred and is occurring is actually use that is on label because FDA's traditionally labeled indications for antibiotics are very broad, and allow companies to market these drugs widely to physicians across the country. For example some of these indications include treatment for respiratory infections or skin and skin structure infections. Not surprisingly, marketing works and the drugs are then prescribed widely in ways that are not approved.

Some of these widely marketed drugs might be extremely useful against treating serious infections but instead are being used to treat more common infections or infections where alternatives exist. All this is in compliance with the existing broadly worded FDA indicated label. Such broadly used prompts development of resistance and is problematic. LPAD drugs will include narrow indications that are much more consistent with antibiotic stewardship principles. There are also built in protections that will further limit off label use of these drugs.

First is the advancement of the antibacterial stewardship programs across the United States, which we need to, continue to support. Stewardship will preserve LPAD drugs and will help to protect patients from inappropriate use.

Second, built in protection is the premium pricing expected for LPAD products. The marked difference in these drugs versus other agents will reduce LPAD off label use particularly if premium reimbursement models restrict reimbursement to on label use only.

Third, medical liability concerns would deter physicians from using these less well studied drugs off label.

Fourth, most of these agents will not be in pill form, there will be no opportunity to use them for more common outpatient infections.

The final point is absolutely critical that off label use for LPAD drugs not be banned. Off label use of antibiotics typically occurs when physicians are confronted by problems that on label drugs are not equipped to handle.

Patients will be harmed if off label use is banned. For example, an antibiotic that treats KPC klebsiella in the lung and blood is approved via LPAD. A patient develops KPC klebsiella infection in the brain. His or her physician should not be banned from using lifesaving drugs for the infection. If we want to reduce inappropriate antibiotic use, the key is not to create enforcement mechanisms that target off label use. It is to control the label as LPAD does, to ensure that on label marketing is more narrowly targeted. Thank you

RACHEL SHERMAN: thank you for your comments, questions from the panel?

EDWARD COX: thank you for your comments Bob, I'm just curious, you touched on this, if you can just speak for another minute on the issue of LPAD availability with drugs through the IDSA proposal and balancing risks and benefits and essentially what this could mean for patients with unmet needs.

ROBERT GUIDOS: I think from a physician perspective, there are, and for patients who have the most serious severity of illness, of these bacterial infections. Again, there are various levels of dosing, using your diagram here, I mean a growing level of severity and the very severe patients, we need to create a mechanism to get those drugs to patients with most severe or serious infections. For those patients with those more serious infections, I think the patients themselves and physicians will be more tolerable of using drugs that efficacy and safety profile are less well characterized

EDWARD COX: on the question of achieving appropriate use, wondering if you might comment on any role that you might see for IDSA here as far as achieving appropriate use, which dovetails with stewardship also.

ROBERT GUIDOS: as was mentioned earlier, there's a role for IDSA, a role for the society of infectious diseases, pharmacists, the society of healthcare, epidemiology of America all of which focus on developing and supporting metrics of appropriate use and those are lumped under what is called today, antimicrobial stewardship.

Even though physicians may not see the label, the pharmacist will see the label. The formulary folks will see the label and understand how these drugs; that these drugs are ones that are particularly of concern. We need to be using them wisely and how to use them wisely. So there needs to be a way to build within the antibacterial stewardship programs in each facility, ways to do that.

If it means showing the physician how expensive these particular drugs are, that's one way, or having more active role of the hospital administration. As far as IDSA and SIDP, I think from our perspective we'll be working with CDC and the FDA to help educate physicians and healthcare providers and others about what these about what this new category of drugs is. Again, that the risks are not as well characterized as traditionally approved agents.

ISSAM ZINEH: I just want to clarify that I heard loud and clear that the FDA should not put restrictions on use other than carefully controlled labeling language. And this is a general principle. Can you envision any situations in which restricted, some sort of limited restriction would be something that could be reasonably expected to be used?

ROBERT GUIDOS: so I think we are very happy to work with, discuss potentially what other mechanisms could potentially work in this area. As far as a REMS program, there might be some REMS ideas that are worth pursuing or considering. I don't have any particular suggestions today.

RACHEL SHERMAN: other questions?

DIANE MALONEY: just a question, I think I heard you say the products ought not to be used in less serious infections or where there are alternatives. The FDA ought not to get involved in off label so how do you balance those two?

ROBERT GUIDOS: can you say that one more time?

RACHEL SHERMAN: I think I have a similar question to Diane's. Correct me if I'm wrong, we're talking about antibacterial here; probably a vast majority is prescribed by non-id physicians, so FDA, it sounds like you don't believe that stewardship belongs to either with the company or the agency. FDA would carefully craft labeling that would outline the appropriate use. What happens if we are able to track it and document that in fact, there's a substantial level of what we call inappropriate use? Is that what you are asking?

ROBERT GUIDOS: I think at that time it would be an opportunity to work with the healthcare community to look for opportunities, and with centers for disease control, to find ways to make sure these drugs are put to use more appropriately.

RACHEL SHERMAN: not that you need to answer but like what do you do proactively versus after you get the information? So I think what I'm hearing you saying is well let's see what happens and then if need to do something, people could do it then? Thank you.

Thank you for your comments, the next speaker is Paul Huckle from Glaxo Smith Kline

PAUL HUCKLE: Dr. Sherman, Panel, good morning. I thank you for the opportunity to speak. I am Paul Huckle; I'm the chief regulatory officer and head of regulatory affairs for Glaxo Smith Kline. Glaxo Smith Kline applauds the FDA's efforts to explore the potential advantages and disadvantages of creating an *"Alternative Approval Pathway for Certain 'Drugs Intended to Address Unmet Medical Needs."*

This alternative approval pathway appears to be consistent with congress' intent with the GAIN act and the PCAST recommendations, to encourage development of new therapies. If properly designed and implemented, such a new pathway might well help to develop improved development and rapid delivery of new antibiotics to patients with serious and life threatening illnesses. It may be especially useful where the feasibility of conducting one or more large

clinical studies is not possible, through a variety of reasons. For example, in some populations, limited patient numbers, such as can be found in the areas of rare diseases, oncology and infectious disease.

GSK is committed to supporting the appropriate use of antibiotics and exploring new models to sustain the discovery of novel agents whilst the details of any new proposed pathways still need to be defined, GSK believes that such a pathway could in principle be an important step in revitalizing antibacterial medicines, discovery and development. We further believe that the proposed pathway may help to address other infectious diseases with higher unmet medical needs, such as severe influenza where hospitalized patients fail to respond or are unable to respond to existing therapies.

GSK has been encouraged with ongoing discussions with the agency, and with FDA's willingness to be innovative in evaluating antibacterial drugs aimed at patients infected with multi-drug resistant pathogens. If implemented, we will consider adopting such a pathway in the clinical development of our own pipeline antibiotics for treatment of hospitalized patients with serious or life threatening infections caused by multi-drug resistant pathogens.

We believe that the proposed pathway should be considered in parallel, and in addition to, already existing regulatory pathways such as Accelerated Approval, Fast Track, Priority Review and Breakthrough Therapy Designation, and if implemented, should be applied at the sponsor's request.

Whilst existing regulatory pathways provide the agency with some flexibility in dealing with the review and approval of medicines, such a new pathway could further encourage the development of medicines for small populations, by providing an explicit mechanism for sponsors to gain agency support for novel and streamlined development programs.

An Alternative Approval Pathway may indeed result in an increase the therapeutic options for patients with serious or life-threatening conditions, where there is an unmet need. Such therapeutic areas may include, but may not be limited to, infectious diseases, rare diseases and oncology.

Regarding infectious disease:

For areas of high unmet medical need or public health concern, in which current therapies are not effective, e.g. multi-drug resistant bacterial pathogens, there is still a need to develop antibiotics for specific sub-populations or to undertake pathogen-specific study approaches which may result in restricted labeling.

Considering the unique circumstances surrounding antibacterial drug development, this proposed pathway may prove effective, thereby serving as a testing ground for small patient populations. Lessons learned in this process may subsequently be applied to other pathologies and subpopulations.

It is particularly important for sponsors to be encouraged to conduct studies and to address unmet medical need for diseases in limited populations. Unfortunately, there are examples where high development costs for drugs with limited patient populations, far too often lead to the greater prioritization of other therapies for larger populations. For this hurdle to be eliminated there needs to be collaboration, flexibility and clear expectations between sponsors and regulators.

For example, in programs addressing severe infections, this proposed pathway might explore a "Totality of the data" approach which would include the appropriate extrapolation of pre-clinical data to human efficacy and safety predictions; the use of phase II data and perhaps a small Phase III study. Due to the nature of such sub-populations, it is likely that it will not be possible to obtain comparator-controlled data and consideration should be given to the acceptance of historical control data in these cases.

Small patient populations represent challenges in recruiting and conducting clinical studies. To be feasible, trials may have to be conducted against a background of more limited safety and efficacy data than might be expected in more routine programs. Examples of these challenges will include severe hospitalized influenza, emerging threats such as avian flu and, targeted antibodies against resistant pathogens where there is unpredictability, due to seasonal outbreaks or geographic variability.

Such a proposed pathway could further facilitate development of drugs for oncology and rare diseases across multiple therapeutic areas. For this to occur, the agency should provide clear

Guidance on approaches for acceptable benefit/risk paradigms and specifically what would constitute "substantial evidence" and effectiveness in such small patient populations. Such approaches might include:

Innovative methodologies to demonstrate efficacy & safety in small clinical trials eg use of. non-traditional statistical analysis, the use of modeling and simulation as predictive and evaluative tools in creating feasible clinical study designs. Or reliance on the use of biomarkers and pharmacogenomics and patient reported outcomes (PROs), recommendations on multiple marker diagnostics and drug/device co-development paths in the oncology and rare disease settings.

GSK does not believe that FDA is either authorized or well-positioned to monitor individual prescribers' practice of medicine-including the use of products proposed under this pathway. Neither should manufacturers be required to monitor or enforce the compliance of individual prescribers or healthcare institutions. If this *Alternative Approval Pathway* proposal is to be viable, clear boundaries of authority must be drawn so that FDA does not intentionally or unintentionally encroach upon the practice of medicine.

Informative labeling of products approved under such a pathway should summarize the available data; indicate limitations of these data and areas of residual uncertainty. Appropriate prescribing of these products remains the responsibility of trained physicians who need to be able to use their medical judgment to determine the appropriate treatment for individual patients.

GSK believes that the infectious disease community (including individual prescribers, pharmacists, healthcare institutions, professional associations bears a responsibility for monitoring antibacterial drug use, and these best suited to evaluate proper antibiotic use at an institutional level, with respect to antibacterial stewardship. Therefore, GSK believes that the accountability for monitoring, prescribing practices and/or tracking clinical practice should reside at the community level. Approaches may include the use of formularies, clinical practice guidelines, hospital use protocols and training.

GSK has committed to proportional promotion, supporting appropriate prescribing at the right dose for the right duration, as well as communicating the risk/benefit profile of our antibiotics to the infectious disease community. Where appropriate, and where necessary to ensure that a

specific product's efficacy for its labeled use outweighs its risks, patient registries or other elements to assure safe use, could be employed as part of approved REMS.

However the universal application of REMs -type requirements to all special medical use approvals, is likely be an ineffective strategy toward antibacterial stewardship, and would needlessly burden an already over-burdened healthcare delivery system.

We believe if implemented, the FDA should work collaboratively with sponsors and the health care community to ensure that prescribers are aware of the unique prescribing considerations of products approved under this proposed pathway. For example, clear logos and "restricted use" labeling on package inserts, container labels, and packs would help to ensure that practitioners' attention is drawn to the limited nature of the special medical use approvals.

Finally consideration should also be given to establishing training programs on the appropriate use of products approved under this mechanism and labeled as such.

Thank you.

RACHEL SHERMAN: thank you for your comments. Questions?

EDWARD COX: Thanks for your comments. I was wondering if you touched on this somewhere in your points, on the availability of such an approach, and how that would impact on the development decisions that a company might make particularly in the area of unmet need.

PAUL HUCKLE: Yes. So in the current framework, sponsors have to invest significant resources to develop these products without explicit understanding around what would be an acceptable benefit-risk for patients in these particular settings. The acceptance of risk or uncertainty in these areas for these populations would be quite different from a more routine program. It's very difficult for a sponsor to anticipate the start of a very long development program while that judgment would be at the end of the process when the product goes to review, to the extent any such framework helps to shed light and produce more clarity around expectations that would be helpful.

DIANE MALONEY: I just had a question about the proportional promotion. Is that something you do for all your products or is this something special that you are proposing.

PAUL HUCKLE: No. Clearly there's an obligation on sponsors to appropriately promote all products. The comment I make is that under this particular pathway, where the approval would be more restricted or limited, than would normally be the case, that would feature in the way the companies would go around promoting the product so that it was explicit that these products had more restricted labeling than products that might have been approved under a broader remit. Either way, clearly, the sponsor is obligated to promote more specifically in line with the label.

RACHEL SHERMAN: could I follow up on that? How do you envision that working? Do you envision that FDA would have different enforcement authorities for these products? Is this voluntary or part of the company, how do you see this playing out?

PAUL HUCKLE: so I think the standard practice in terms of how the company would go around promoting products and how the agency would oversee that would be consistent with what commonly occurs now. What I'm highlighting is that where there is much more restricted label, we would need to be very explicit to prescribers; this product was approved under this particular framework. That is why the label is restricted, through absence of data. And clearly, it would be incumbent on the sponsors to draw the attention of potential users to that.

RACHEL SHERMAN: so sorry, remembering what we heard from the Parkinson's community, it sounds like you envision the agency putting very prescriptive language in the labeling. We can only enforce against labeling, about obviously not prohibiting or touching off label use, saying how restrictive it is, will be the only appropriate way. Do you have concerns about the impact of reimbursement with that?

PAUL HUCKLE: So let's be clear, the label would have to reflect the data on the basis for which the approval was made and as a part of the labeling language, it would be clear that these data existed and specifically other areas that were explored because the data was not available. In terms of reimbursement, I think we come back to the discussion the previous speakers made around the pricing reimbursement for products for limited use small patient populations as products tend to be. Better priced and reimbursed, obviously reimbursed against very specific smaller populations of patients.

RICHARD KLEIN: I just had a quick question. I suppose we would take that down one step. It was the point about the responsibility moving down to the community level for monitoring use and using formularies. I think from my experience with lots of restrictive labeling, and efforts on the part of the FDA to communicate risk and uncertainty, there's still a lack of control of things that should be much more controlled, wondering if you have an example of this type of paradigm that has been successful.

PAUL HUCKLE: I think in the area of antibiotics, as we have heard from many of the previous speakers, the concept of antibiotic stewardship is pretty well developed and in place in many of the institutions that use these. I think the combination of appropriate from the FDA approval, where necessary, augmented by med guidance, such like, the appropriate promotional, the education from the sponsor and then the underlying basis of antibiotic stewardship that is inherent in the institutions and the way the products are intended to be used by the community. I think that overall presents a pretty good way of managing use of these products in the antibiotic space.

ISSAM ZINEH: you mentioned that there should be considered in the context of already existing paradigms like fast track, priority review, breakthrough designations. Most of those are administrative in terms of the flexibility offered, although there is some element of evidentiary flexibility in some programs. I'm trying to create some granularity, maybe around the comments that you had. Do you see, this new pathway being more of an administrative pathway or evidentiary pathways? And would you do something different than what the current tools would do?

PAUL HUCKLE: so I think there's a significant amount of flexibility that the FDA can operate using the existing approval paradigms they have. I think potentially, an additional value this would bring is a very explicit framework that says, if you have a product that is in a program under this pathway that is review and approved in this pathway, there's an expectation that is would have more limited data to get approval and it would consequently have more limited labeling in terms of the final product approval. So I think it is being more explicit around this type of development for these types of patient populations versus retrofitting this approach into the existing alternative regulatory pathways.

RACHEL SHERMAN: thank you for your comments. Our next speaker is Jennifer Jackson, Cubist pharmaceuticals

JENNIFER JACKSON: I'm Jennifer Jackson, Senior Vice President, Regulatory Affairs, Cubist Pharmaceuticals. Cubist is a biopharmaceutical company focused on the research, development and commercialization of pharmaceutical products, especially antibiotics that address unmet medical needs in the acute care environment. We currently market CUBICIN[®] (daptomycin for injection), the first intravenous (IV) antibiotic from a class of anti-infectives called lipopeptides. In the wake of a successful launch of CUBICIN, the company has a growing pipeline that includes antibiotic candidates to treat difficult infections including those caused by *Clostridium difficile* and Gram-negative bacteria, such as drug resistant *Pseudomonas aeruginosa*.

Cubist believes that today's public meeting is another opportunity for innovative companies, patients, and specialists to cooperate with the FDA to enhance innovation and encourage the development of new antimicrobials. We are pleased that the Agency is not only acting quickly to implement the Generating Antibiotic Incentives Now (GAIN) provisions included in the Food and Drug Administration Safety and Innovation Act (FDASIA), but also looking ahead aggressively to identify other measures that can accelerate innovation.

We wish at the onset to applaud Dr. Woodcock last year to Congress. To quote to "continue to work with patients, health care providers, academia, [and] industry, to modernize the paradigm of antibacterial drug development through guidance and clinical trial designs, and to seek additional solutions to the challenging scientific issues facing the field of antibacterial drug development. We cannot overstate our agreement with Dr. Janet Woodcock's sentiment that Congress and FDA must continue to pursue specific improvements in federal law and policy before we can achieve greater progress against resistant infections.

To that end, the concept of an "alternative approval pathway for certain drugs intended to address unmet medical needs," is an important reform that could accelerate antimicrobial innovation. It stems from Dr. Woodcock's leadership and that of Dr. Rachel Sherman, Dr. Ed Cox, Dr. John Farley, and their colleagues in the Office of Antimicrobial Products, and their engagement in years of discussions with sponsor companies like Cubist and specialists like the Infectious Disease Society of America (IDSA).

Two years ago, building on these discussions, the Agency convened workshops on antimicrobial resistance and on the design and conduct of clinical trials for antibacterial drugs, which helped lay the conceptual foundation for today's hearing. Just last year, Congress heard testimony on the proposed creation of new statutory authority for "limited population antibacterial drugs" (LPAD) during consideration of FDASIA. Cubist was integral to those deliberations, and we view today's meeting as an important continuation of efforts to refine and achieve consensus on this proposal.

It's no exaggeration to say that our collective failure to adapt and employ flexible regulatory approaches will only compound the economic and scientific barriers that have driven sponsors both big and small away from investing in anti-infective R&D in favor of other, more financially certain therapeutic areas. To be specific in responding to question 2, creating an alternative approval pathway could greatly enhance prospects for successful clinical development of novel antimicrobials against those deemed by leading infectious disease specialists as the "ESKAPE" pathogens² and many, though not all, of the pathogens targeted by Congress in the newly enacted definition of "qualifying pathogens."

Cubist believes strongly that, properly designed and available to sponsors at their discretion, such a pathway would be an important complement to the market incentives and regulatory reforms already enacted and being implemented by the Agency as the GAIN Act.

Cubist believes that an "alternative approval pathway" for antimicrobials is best understood as consistent with, and complementary to, the many ways that the FDA already exhibits science-based flexibility in addressing unmet medical needs for serious and life threatening conditions, such as its regulations, policies, and guidance for accelerated approval under Subpart H, Fast Track approval, and orphan drug development for the treatment of very small patient populations.

The FDA should adopt a tiered regulatory framework that allows either disease or pathogen-based label indications, along with labeling that encourages the most appropriate use of new drugs commensurate with the approved indications. Such a framework is wholly consistent with the FDA's current regulatory approaches to accelerated approval, Fast Track, and orphan drug development. Such a framework would encourage sponsors and the FDA to collaborate and

identify clinical development programs that balance the quantity of data required for registration with the unmet medical needs in the areas of antimicrobial resistance and novel and emerging infections.

As with Fast Track review, an alternative approval pathway should be initiated upon a sponsor's request and FDA's agreement. Encouraging sponsors to pursue clinically challenging as well as economically challenging development programs for antimicrobials is only possible, where the sponsors may elect to enter into alternative reviews by the Agency.

Cubist believes strongly the pathway would not be feasible if it were imposed on sponsors, rather than made available to them as a potential development and review pathway. Historic experience with other expedited approval pathways demonstrates conclusively, that collaboration between sponsors and the Agency is indispensable to success and ultimate product approvals.

In response to questions 1 and 4, Cubist believes that approval for smaller populations is possible on the basis of a pathogen-based approach, under which clinical investigations explicitly balance tolerance for the limitations of smaller focused clinical datasets against the severity and importance of the unmet need addressed. Pathogen-based indications are not new: linezolid is indicated for vancomycin-resistant *Enterococcus faecium*. But what is new is the idea of standalone approval solely with such an indication.

In response to question three, when small efficacy studies are conducted, supplemental strategies are likely required for an adequate safety database. Approval will be supported by preclinical evidence of effectiveness, with confirmation based on limited demonstrations of clinical activity. "Supplemental strategies" for such products could consist of a confirmatory phase IV commitment or limited patient safety registry.

Under this tiered approach, the resulting initial approved labeling may clearly summarize the available data, the limitations of those data, and emphasize the importance of the use of the approved drug only when the target pathogens are proven or strongly suspected.

Promotion of the agent should be regulated in a manner that is aligned with the limitations of available data. As initial clinical experience accumulates, it will be important to ensure adequate

monitoring to detect emergence of any safety signals, and as further studies are conducted, the labeling can be modified accordingly.

In response to question 6, a novel mark or logo designating a drug approved under such an alternate approval pathway would not contribute to public and provider understanding of a drug's uses, benefits and risks. Indeed, under this reasoning, such marking would be appropriate for the vast majority of drugs approved or licensed under Accelerated Approval, or for orphan drugs. A new, unproven logo would have limited utility, since the Agency has sufficient authority to approve drugs under the proposed pathway with labeling that may include any necessary assertions or statements that their approval is on the basis of limited clinical information.

Cubist encourages the Agency to make use of the information obtained during this public hearing to advance its thinking and fulfillment of a requirement imposed by Congress in the GAIN Act, as part of FDASIA. If the Agency can promulgate meaningful guidance in the five months as specified by FDASIA, incorporating the concepts we have endorsed, it would be a significant achievement and an important contribution to expediting antimicrobial innovation.

In closing, we believe that FDA is taking positive steps to implement the GAIN Act, and agree even more can be done to accelerate innovation. Approval for smaller populations on the basis of pathogen-based indications, with full weight given to the severity and importance of the unmet medical needs being addressed, should be pursued by the Agency to allow all stakeholders an opportunity to further collaborate with the Agency in establishing a new pathway.

Labeling of such drugs could provide the basis for approval, and limits to the clinical data, and assure their appropriate use against the target pathogens. Such an approach would afford sponsors and the Agency alike a spectrum of development programs and pathways that could greatly facilitate the availability of important new drugs to combat novel and emerging infections, and those resistant to multiple antibiotics.

We appreciate the opportunity to speak today, and look forward to continued collaboration with the FDA in meeting the challenge of antimicrobial resistance and serious and life-threatening infections. Thank you.

RACHEL SHERMAN: Thank you for your comments. Questions from the panel?

EDWARD COX: Hi Dr. Jackson, thanks for your comments. Just wondered if you might comment a little bit more on the issue of the role of the pharmaceutical companies in achieving appropriate use; that's for a drug developed through a limited use program.

JENNIFER JACKSON: I think the role of the pharmaceutical company at this point in this new paradigm, would be very similar to what it is today given appropriate messaging, appropriate education, to both the prescribers, the community and the institutions.

RACHEL SHERMAN: I have a question, following up on my question on promotion, your comment about supplement of safety databases, let's say we have a very small pathogen based population, and there's a supplemental safety database, what do we do with those data, are they in the labeling and how would that impact promotion?

JENNIFER JACKSON: As new safety data emerges, as with any program, that data should be added to the product labeling and then as such would be part of any education or communication about the product.

RACHEL SHERMAN: would the company be able to promote the product, presumably the safety area is derived from a population different from this small pathogen group. How will that be handled in the promotion; say there was 300 patients studied with uncomplicated UTI that's not the indication, what would happen with those data and how would see the company handling that promotion.

JENNIFER JACKSON: so let me see if I can understand your question; your question is that you have a more complex label that has a broader indication plus pathogen specific indication?

RACHEL SHERMAN: no actually it's the reverse. It's a very narrow indication; 30 patients, 100 patients, however, some multi-drug resistant pathogens. But it was only 100 patients, so a supplemental safety database was derived from patients with urinary tract infections with susceptible organisms. How do you see that results, linked in together with labeling, informing practitioners about the product and how do you that impacting promotion?

JENNIFER JACKSON: So a supplemental database, I'm not imagining that would just be a new tier that that in fact would be something that was developed as the product was used. But in any case, when you're talking about the indication for these seriously ill patients with unmet medical need, the safety that you talk about would be in those patients.

RACHEL SHERMAN: Can I ask you, I didn't get a chance to, since we are ahead of time, who owns stewardship in your mind?

JENNIFER JACKSON: I think this is something that is owned by society but it very carefully is the purview I think, of the treating physicians and the hospital where these patients are being treated. These are not patients with ear infections, these are patients with very serious infectious without appropriate therapy available to them. So I see it there in the hospital.

RACHEL SHERMAN: do you see it as voluntary, and if you will local action, not coordinated in any one entity.

JENNIFER JACKSON: well, certainly as Dr. Guidos talked about IDSA and those other groups, education by the pharmaceutical company could also add to that.

RACHEL SHERMAN: Thank you. Our next speakers are John Crowley, John Kirk, and Jayne C. Gershkowitz from Amicus Therapeutics.

JOHN CROWLEY: Hi, good morning, thank you for the time. I'm John Crowley the CEO of Amicus therapeutics. Also joined by as you indicated is John Kirk, our head of regulatory affairs as well as Jayne C. Gershkowitz, who is our head of patient advocacy. I'll be speaking for the first few minutes and then we'll defer to Dr. Kirk on some specific proposals. We at Amicus work in the field of rare and orphan diseases, primarily in the lysosomal storage disorder field. And as you know there are many approved therapies in this disease field.

When the announcement of this public hearing came out, we felt that it was important to be able to speak to the other side of the panel. And it's important that there' been a lot of discussion about infectious diseases and potentially even some indications here and opening that end of the

funnel. We also thought that it would be important to highlight in the rare diseases, where this could be used and let me state that at the onset, that we always want to work with the FDA to create new pathways for medicines to get to patients quicker. And in the rare disease field, and again in the lysosomal storage disease field, particularly, there have been therapies approved.

There are many examples we could give however, there are specific sub-populations of these diseases where there are still significant unmet medical need even in areas where there are approved therapies. We can highlight many even within the LSD's for instance type 3 Gaucher disease, even though there has been an improved enzyme therapy for more than 20 years now in gaucher disease, people still struggle, suffer with and die from type 3 Gaucher, the neuropathic form of the disease.

One example I will highlight for you this morning is in the area of Pompeii disease and as you know Pompe disease being LSD, is also one of the muscular dystrophies; a disease characterized by the buildup of glycogen in the lysosome, heart, skeletal muscles. The first clinical studies in this disease were in 1999 for an enzyme replacement therapy; a therapy that went on to be approved in the form of its trade name, myozyme in 2006.

First clinical studies in that disease was in a little more than a dozen patients, a very small clinical study with clinical endpoints timed to ventilator free progression on survival. If you fast forward now we are about seven years since the approval of myozyme, and the pictures that you see here on the screen actually represent 5 different patients, all with pompe disease, all currently on enzyme replacement therapy. And as you can see they represent the spectrum of this disease; a disease that is thought to occur in about 5 to 10,000 patients in the developed world, several thousand here in the United States.

I come here today as CEO of a biotech company working in the rare disease field but also as a dad. And the first picture on the left you see are my two children; Megan and Patrick who were diagnosed in 1998 with Pompe disease, again receiving an experimental therapy in 2003 and now just more than a decade later remain on that therapy. And like many patients in pompe, it saved their lives, its improved their lives but it's far from the last answer for this disease.

And if you look at the examples here, Megan was fifteen months old when diagnosed, Patrick seven days old. In the middle we have patients with the adolescent's form of the disease just diagnosed in the last three years. They look like normal kids but they still suffer with significant muscle loss, and loss of function, again both on enzyme therapy. And then on the right, a gentleman with the adult form of pompe disease. And even after enzyme therapy had to spend four and a half years in the hospital till he could go home.

One thing common in all of these patients if you want to quantify it, is the infantile, the adolescent, the adult forms of the disease, is in addition to the basic path of physiology of the disease. One of the complications of replacement therapy is the response to the therapy in the form of antibodies,

We know that all people with pompe disease, they all produce antibodies and of course it has a different effect in all cases, it mitigates the effect of the ERT. For infants diagnosed, and even again in the infantile population, you can divide it into crim negative and crim positive. Crim negative means the infants who make no protein whatsoever; the most severe form of the disease. They typically respond quite well to enzyme replacement therapy, mount a robust antibody response which effectively negates all the efficacy of the ERT and often results in death a year or so later.

Physicians including doctors at Duke and other universities have pioneered research in trying to figure out how to deal with the modulation of the immune response here. The commonly accepted approach for infants in pompe disease is the off label prescription of two medications and combinations; methotrexate and pentaxina used to effectively oblate the immune systems of infants with pompe disease prior to their receiving myozyme.

For those children that can survive this brutal immune suppression, it does seem to significantly improve the therapeutic outcomes on ERTs. There are other drugs in development including one that Amicus is looking at the potential and still needs to be explored in local populations. So we think it's important when we talk about the potential use of this pathway to realize, the more and more that we cut these populations, the more and more it is for companies like Amicus and others to do clinical studies with long term clinical outcome. And we think this is a very good idea for the FDA and it could be explored and used very effectively in the field of rare disease

including in the field of pompe disease especially where there are treatment options and approved therapies are significantly limited.

I think the statement from PCAST, highlights some of what we're talking about here including at the very end where they talk about this type of work being linked to the quality of information that can be acquired after a drug is in the market. We can envision a future in many of these rare diseases including in pompe where we can do small targeted studies in very defined subpopulations of patients with these diseases, perhaps based on surrogate markers which can lead to accelerated approval with a very strict and well controlled label.

And I think that's the responsibility ultimately of physicians to be fully informed but I think there is a significant burden on companies like Amicus and others to be able to provide the information necessary, for physicians and the tools, so that they can make the informed decision on how best to treat patients. We have several other ideas and I'll ask Dr. Kirk to step up here for just a few minutes and to share those out with the panelist. And as well we'll be both available to take your questions. Thank you.

JOHN KIRK: Thank you John. My name is John Kirk; I'm vice president of regulatory affairs and quality assurance, Amicus therapeutics. Thank you for the opportunity to present today, I appreciate it. I think this is an important public health issue. Today I'm going to give you an illustration only on what's possible in terms of implementing expedited approval pathways and compare generalized requirements of what industry would generally consider as conventional as opposed to what could be considered expedited under the provisions of the context in which we're talking today. In particular I'll address 3 areas; in particular in manufacturing control, preclinical safety testing and regulatory approach in interacting with the FDA.

So this slide on the left column in manufacturing control and conventional sense if you think about it, we always think three registration batches, three process foundation batches and so forth, and whatever number imaginary batches occur prior to that. What this results in for companies is an over production. So you have this inventory sitting around, and is that really necessary? In addition, conventionally speaking, the registration batches are not currently available so they are there for other things. Whether that is formulation development, other clinical testing, whatever, the materials are not available commercially.

ICH guidelines, with respect to stability data, expiration date in general require real time so a two year labeling expiry date, requires two years of data, so it's not possible to give that with an accelerated conditions. If you look at it from an expedited perspective, rather than thinking of three batches, you can apply what is referred to as continuous verification. And what you're trying to do is you're trying to achieve adequate state of control in the manufacturing process. And that's fine; it doesn't necessarily need to take all of these numbers of batches to get there. At the end of the day, you're pre-approval inspection ready just as you would be in a conventional sense. So you arrive at the same place but you're doing things in a more continuous fashion.

To enable the commercial use of earlier batches, that would be useful. And maybe a few batches represented in an MDA especially in a narrow population like this, doesn't necessarily make sense to have ten batches or whatever, in an MDA.

With respect to the stability data, we want sufficient stability to cover the shelf life of the drug, when the two years based on projected commercial supply needs, which are going to be low and we know that, so it would be nice to tailor the manufacturing to the need in the market.

Preclinical safety, in the conventional sense, you're looking at the ICH guidelines, you're looking at things to enable first in human studies in phase one, then things you have to do in phase two if you want to do studies in children, you have to do infantile toxicology and of course if you have a small molecular, you are looking at two years, and if a drug is not particularly toxic, you are talking about many, many kilograms of material in a two year rodent study, rats in particular.

If you do this in an expedited fashion, you want requirements to support specific sub sets that you are talking about. So we'd like to in this subpopulation stop using the term phase 1 and 2 and 3 and 4 because it doesn't really fit. And then you have to look at that therapeutic gain and how do I achieve that. And how do I show that I have enough preclinical data that is safe to proceed in a clinical trial. If you have waving infantile toxicity, for example, if you have sufficient data in adults, this may not be necessary as an investment. And then studies would be lower in these than were deferred in phase 4 as a rule.

And the regulatory considerations are in the conventional sense; they differ by region. The Europeans have a very different way of looking at things in these rare diseases compared to the FDA in the US. So you're always having serial meetings, you're always working to get your guidance to converge, and sometimes it doesn't. But we always need one global strategy because you can't do two programs for the role. And we understand that, in principle, labeling would be a large end scope in the conventional setting.

From the expedited point of view, we'd like to have one single global strategy based on the geographic distribution. What are those patients, which agencies are involved and can we have the sponsor and government on a common development plan. And we recognize, that the labeling will be narrow, we understand that it is going to be targeted to the specific subset that you're talking about in the endpoints you sued and we know that.

And of course as additional data comes on, you can expand the labeling. There will be concern around reimbursement but that is a separate discussion point.

And lastly, in terms of conventional approaches to given guidance from FDA, we're in the maps here, we have types A, B and C. and we all know that we have the codified meetings inter-phase 2 , pre MDA and so forth. These briefing documents that you have to write for these meetings are lengthy, they can take several months to write, and they are complex. The review cycles are standard priority, we understand that additional months added to that first action, and we know that too.

If you looked at this from an expedited point of view, again just like phase 1,2,3 and 4, put that aside, put aside type A,B,C kinds of meeting too and just have one unique kind of approach. Or you could have a more frequent meeting with FDA, a narrow scope, shortly timed, documents apart, easier to write; in fact your approximate real time in the development rather than large chunks of development at a time.

And, in whatever we do in respect to these, we'd like the guidance to be binding on the divisions. With that, I'll stop there seeing my red light is flashing. Thank you.

RACHEL SHERMAN: Any questions?

ISSAM ZINEH: This is kind of specific, but we heard approaches from some of the other speakers that some of the preclinical data can really serve to augment the clinical and in some cases, albeit the need for clinical, something about the animal as a potential proposal. And so I would probably, you can interpret that to say that heavy reliance on mechanistic information might give regulators and the public and even developers more confidence that the drugs are likely to be active and safe in the population that will be exposed; whether it's the targeted indicated population or those who will be exposed off label. But in your proposal, it's much more abbreviated; I guess you're trying to get some sense that you can move into the clinic as opposed to getting a full scope of what the toxicity profile might look like once people are exposed. Can you reconcile that a little bit against what we heard from the other speakers earlier?

JOHN KIRK: well I can try a little bit. The first thing I would do is differentiate animal models of efficacy from ICH toxicity and testing under GLP conditions. In the first sense, I agree completely that there are ways in anti-infective in particular; it's probably very rational to use short animal models to do that. In terms of the safety testing, I think we're just looking at, not just at the necessarily having to do very, very long toxicity studies especially if you're looking at a timeframe, treatment where life expectancies may be shorter; it doesn't make a lot of sense to do that.

I think, and also I'm not saying that we would not do any preclinical safety testing. I think the point is to do sufficient preclinical toxicity testing, in the appropriate species to support what we're proposing to do with humans. Rather than just following ICH guidelines right down the line; I'm looking at it as a flexible point.

RACHEL SHERMAN: Question, are you envisioning this paradigm parallel in terms of a breakthrough product. It's what it sounds like to me.

JOHN KIRK: Yes.

Rachel Sherman: Stay tuned there'll be guidance. Thank you.

Our next speaker is John H. Powers, George Washington University School of Medicine,
University of Maryland School of Medicine

JOHN POWERS: Thank you for the opportunity to testify at the meeting today, in order to represent the patients for whom I care as well as the clinicians and physicians who look up to the FDA for adequate evidence in order to better treat their patients. Just in background, I'm infectious diseases and internal medicine physician and a clinical investigator who cares for patients in the hospital setting, many of whom are critically ill. I'm also a former lead medical officer for antimicrobial drug development and resistance initiatives at FDA, and a former co-chair of the inter agency task force on antimicrobial resistance.

FDA scientists are dedicated public servants who do their best to promote the health of the public and hopefully this discussion today will help them to advance that mission.

Much of the discussion today is revolved around what goes into drug labeling. It's worth remembering that what goes into labeling determines what drug companies can advertise and sell their products for.

Drug labels do not regulate the practice of medicine but if clinicians choose to use the drug in clinical practice that is a decision between them and the individual patient as a part of the practice of medicine.

However drug companies being allowed to market a drug of un-cleared safety and efficacy, merely because clinicians and patients are often left in a position of having little evidence does not mean that having little evidence to be the standard for drug approval.

The benefit of this limited approval pathway remains unclear because it lacks specifics in terms of what defines unmet medical need, how FDA will interpret serious and life threatening disease, and how information will be communicated both to caregivers and patients about the limitations of the evidence. The proposal also lacks specifics regarding how this interacts with other FDA accelerated approval programs and any specifics regarding pre-submission of marketing materials by drug companies, and any legal or regulatory action that might be taken if companies do promote their drugs for unstudied indications.

Much of the discussion today has been about how patients can get access to new medication. However there has been little discussion about how this program would interact with other

pathways such as emerging CIND, treatment INDs, merchant use authorization that might allow patients to get access to these medications before full approval.

Giving this lack of specifics, it is unclear if this pathway would increase therapeutic options. However this question does not get at the heart of the matter. Patients need safe and effective options that are superior in effectiveness and or safety to drugs that we currently claim are ineffective today. That is where the unmet medical needs lies.

The recent history of antibiotic development shows that many drugs have not met these unmet medical needs. 50% of antibiotics approved since 1980 have been withdrawn from the market exceeding any other therapeutic area. This analysis shows that one third of those drugs were withdrawn for either lack of efficacy or safety issues including five drugs in a single class. Two thirds of them were withdrawn because of poor marketing sales. Many times the first in class drug remained marketed, so the follow on drugs did not address an unmet medical need. And the remaining drugs had the same resistance patterns as the drugs that were withdrawn. So these withdrawals were not due to emerging antimicrobial resistance.

In order to ensure that new drugs meet unmet medical needs, FDA should adhere to its own high standards of substantial evidence from adequate and well controlled trials. Drugs can then called including today for approval based on case series supported by modeling. However patients with a resistant infection often are critically ill and the ability to analyze such case series is as very challenging giving multiple confounders.

Indeed drug companies have argued that often patients die of other things and therefore superiority trials might be challenging. But if new drugs don't prolong life or decrease irreversible morbidity, then they are not meeting the unmet medical need. It seems clear that saying a drug is lifesaving should be more than a euphemism and there should be adequate and well controlled evidence to show that the drug indeed saves lives.

Surrogate endpoints are less needed in acute disease for actual benefits, on how people feel, function and survive, can be measured in a short period of time. And surrogate endpoints are often used only when the treatment effects of the intervention are small. Which raises the

question, should this pathway really be reserved for agents in whom the treatment effect is large on the irreversible morbidity and mortality.

In addition several legal precedent point out the challenges of accepting data from case series. In 1970, the pharmaceutical companies sued the FDA about their inadequate and well controlled standard. And in those legal cases, the courts made clear that isolated case reports, were not a basis for approving drugs. In addition, FDA's own current regulations point out that uncontrolled studies are not acceptable as the sole basis for claims of effectiveness. Again this is linked to the scientific challenge of being able to analyze data in very clinically ill patients in whom there are multiple confounders.

Legal precedence also point out that these standards are minimal requirements for any study to yield meaningful results. We can take some lessons from early studies of antibiotics. Kohlberg and Kenny's studied sulphur drugs in 1936 in sepsis in pregnant women, a group part usually young and healthy with few confounding illnesses. They studied only 38 patients with sulphur drugs and compared them to an external control group of 38 patients who did not receive the drugs. They showed a marked decrease in mortality a decade before randomization was first used but they attempted to make sure that the patient characteristics between the treated and the untreated groups were similar. They showed decreased mortality in the treated patients but their own conclusions said, quote 'while therefore there would appear to be a very considerable reduction of the death rate with protaxil treated patients, it would be unwise to assume on the basis of so small a series, that the reduction will be maintained' unquote.

Further discussions of unmet medical need; seem to imply that lower standards are acceptable. However, legal and ethical principles of 'first do no harm', show that the Food Drug and Cosmetic act intended no lower standard for people suffering from serious and life threatening illnesses. Smaller trials are possible with a skew of 50 patients if in fact they have the treatment effect that we would have seen in the pre-antibiotic era. If new drugs have large treatment effects on mortality and irreversible morbidity, this also makes any adverse events much less concerning in terms of a risk benefit analysis.

Finally Kohlberg and Kenny's modeling can be useful in helping to choose appropriate dosing and exposure for such trials but are not a substitute by themselves for data from patients.

Current guidance that is accepted by FDA, international regulatory bodies and drug companies, outlines the criteria for doing such smaller trials including those with external controls. However, smaller populations may be harder to find and therefore may not speed drug approvals. Also we lack the tools to do some of these smaller trials; lack of clinical trials, infrastructure, better diagnostics and well defined outcome measures in order to properly conduct and evaluate these smaller studies. As the institute of medicine documented 2001 pointed out, smaller trials require more planning not less.

Unmet medical needs should be clearly defined and it should conform to other FDA regulations which spell out that serious and life threatening diseases are those that have irreversible morbidity or mortality if untreated.

Another major issue is that to be ethically sound, these studies should be performed in the population who might actually benefit. It is unethical to put patients who do have available options at risk from drugs from which they might not benefit. Without diagnostics, it is unclear how this proposal will be implemented either in clinical trials or in clinical practice.

Unfortunately infectious diseases therapeutics has a long history of inappropriate use of antibiotics as seen as far back by FDA scientist themselves as 1938. The sulphonamide tragedy that was the genesis for the Food Drug and Cosmetic Act when Theodore klumpp evaluated those 105 deaths in small children which showed a majority of them; 100 out of 105 where administered for people who didn't even have an infection.

Labeling alone is insufficient to inform caregivers and patients on the issues associated with drugs and FDA's own experience with other drugs shows this to be true. On the other hand drug companies have used wording in FDA labeling to imply that broader selling of drugs is permissible. While FDA is in the process of rulemaking, the language on suspected infections in 21 CFR 201.24 should be removed as this does not comport with a limited population and clinicians need to be informed. Clinicians do not need to be informed on how to diagnose diseases in drug labeling.

The genesis of much of the issues of declining antibiotic development is scientific challenges in terms of discovering these drugs and also financial. It is not clear that a new approval pathway

will solve either of these issues and paying more for drugs of unclear efficacy and safety seems like an untenable position in a time of increasing health cost.

On the other hand, if a drug actually decreases irreversible morbidity and mortality, then it is well worth its cost. The benefit risk considerations here are very clear, only clinically meaningful effects on irreversible morbidity and mortality justify the increase risk of harm that might be associated with drugs studied in very few patients.

The genesis of the efficacy requirements in 1962 is that the evidence of efficacy needs to be demonstrated first in order to justify any harms of a drug. If the benefits are increased mortality or irreversible morbidity, then many of the issues with labeling becomes much less concerning since adverse effects are less of an issue when a drug truly does save lives based on data from adequate and well controlled trials.

In conclusion, we know the doctors don't read labels, that the labels are not seen in the hospitalized setting, and how will the patients who are critically ill be informed about lesser information and greater risk on these drugs.

Again I'd like to finish up by stating, the label really is a limitation on what drug companies can actually sell for. FDA's own recent history shows that for one quinolone, which first applied for 17 different indications, FDA then attempted to go back and limit the indications because of a serious safety issue with that drug. FDA approached the company and tried to limit the indications to the five most serious diseases; the company declined and took the drug off the market, even though the FDA had concluded that the risk benefit was acceptable, in that those particular more serious and life threatening diseases. So this is going to take some change in the mind set for drug companies as well. And lastly it's going to entail a change in how drugs are reimbursed. Perhaps some of this, the funding for, paying for drugs could go towards actually funding stewardship programs within hospitals that currently do not have ability to do those. Thanks very much

RACHEL SHERMAN: thank you, questions?

EDWARD COX: Thank you John. I was wondering if you might talk for a minute or two, about your thoughts on the issue of the patient population under study, and the two factors of semi resistance being a type of particular infecting bacterial versus patient factors and how that may impact on the assessment and generalized ability of information.

JOHN POWERS: I think that's the challenge, if we take, let's look back at something like HIV which at the time that epidemic occurred was happening in young health people who then ended up dying of bizarre forms of pneumonia we hadn't seen before. Pretty easy to pick out who those people are. If you look at the people who now are getting resistant infections, the available data shows they differ substantially than people who had susceptible infections in terms of being sicker, older, morbidity, and use on other forms of medications. That makes it much more challenging to extrapolate efficacy from one setting of less sick people to a setting of more severely ill people.

Again, I'm advocating, I think that can be done even outside of a randomized trial if you collect the external evidence that shows people really are dying and that the drug actually does increase survival in those settings. But the link is, how do you link that information from what you know in susceptible disease? With clinical information on patients and what you know in resistance diseases.

RACHEL SHERMAN: any questions? Thank you

JOHN POWERS: Thank you.

RACHEL SHERMAN: our next speaker is Nicole Mahoney from The Pew Charitable Trusts.

NICOLE MAHONEY: Thank you. My name is Nicole Mahoney and I'm with the antibiotics innovation project at The Pew Charitable Trusts. Pew develops and supports policies to support antibiotic development and works following the limited population pathway as a potential way to get antibiotics to market. On January 31st, just last week, we convened various stakeholders including the FDA, large and small drug companies, healthcare providers, public health experts and payers to explore the feasibility of this pathway from a business and public health perspective. I'm grateful for the opportunity to address FDA's questions number 1, 2, 3, 4 and 6 and I'll do so based on what we learned from our conference.

All the panelist at our meeting agreed that there is an urgent need for new antibiotics especially to treat infections caused by multi drug resisting gram negative bacteria. Ideally though, a limited population pathway would also help us prepare for emerging bacterial threats making new antibiotics available to patients before resistance becomes common place. The drug makers at the meeting believed that a limited population approval pathway could help bring highly needed antibiotics to market if, it lives up to its promise of making clinical testing more feasible, less expensive and perhaps faster than under existing programs.

If the pathway achieves these goals, it would provide a valuable incentive to companies that otherwise would be discouraged by infeasible clinical trial requirements, lengthy testing timelines, and other factors.

In limiting the market, narrow indications could also allow for premium pricing for high need antibiotics. However, some questions remain about whether or not a limited population pathway makes business sense.

Chief among these are, how will unmet medical needs be defined under this pathway? And what evidence will be required for FDA approval of antibiotics for limited populations. On the regulatory path, there continues to be debate over the extent to which antibiotic effectiveness should be inferred, first as being directly studied in particular populations for example.

Clinical development programs are not the only thing to consider. One of the presenters at our conference emphasized that the regulatory review of chemistry manufacturing, would have to occur on a similar timeframe as the safety and efficacy review, in order for this pathway to work from a practical standpoint. The same is true of diagnostics test to inform their use.

Despite the uncertainty and challenges of bringing needed high end antibiotics to market, we heard from one company that is now planning to develop new antibiotic through superiority study in a limited population of patients with highly resistant infections.

There continues to be debate over whether the FDA could approve limited population antibiotics under existing authority or if legislation is required. But with respect to the impact of the use of these antibiotics, participants at our conference thought new legislation would have a number of

potentially important effects including, sending a strong signal to the provider community about the limited data supporting risk benefit evaluation for these drugs.

This information could impact the management and monitoring of limited population antibiotics. Managing and monitoring were topics we wrestled with most at our conference. We specifically explored the roles of healthcare providers and payers might play to curtail unnecessary use of limited population drugs. Participants indicated that special labels alone would have limited impact on how the drugs are prescribed. There is recognition that initial empiric therapy is the standard of care for many suspected bacterial illnesses and that limited population drugs would often be used empirically. There is no consensus on whether a limited population designation would deter first line use of these drugs.

Some panelist believes that high pricing would effectively discourage unnecessary use because it would increase cost to hospitals, insurers and possibly patients. However, based on levels of inappropriate antibiotic use today and they're high, those involved in stewardship programs across variety of healthcare settings disagree. They notice specific difficulties in managing antibiotic use across healthcare settings especially long term care facilities.

The consensus of our meeting was that effective management of limited population antibiotics would require a broad multi stakeholder strategy. A variety of potential mechanisms were proposed including guidelines on the use of limited population antibiotics, by formulary committees and professional societies, aggressive education of healthcare stakeholders including the full range of potential prescribers, pharmacist, hospital administrators and even patients.

Effective antibiotic stewardship programs across healthcare settings, monitoring and mining of electronic health records and other databases, to determine how these drugs are prescribed and to inform clinical management.

Precertification of institutions where drugs approved through this pathway will be prescribed. Limits on the promotions of these drugs, and the inclusion of limited population antibiotic use in CMS hospital quality reporting measures and or CMS conditions of participation.

That said, within the context of antibiotics, there was consensus among doctors and drug companies that it's not in patients interest for FDA or insurers to actively restrict all off label use of limited population antibiotics.

The panelist decided that some data driven off label use would be appropriate and there needs to be some flexibility in prescribing. Furthermore, because delays in administering antibiotics, impacts morbidity and mortality in patients with serious or life threatening infections, drug management tools such as prior authorization, were not considered an effective way to manage limited population antibiotic use. Some empiric use of these drugs might be expected. The challenge would be to detect and correct unnecessary or inappropriate use when it's detected.

We also explored whether payers, private insurers and CMS could influence the use of limited population antibiotics. We heard that as the current reimbursement mechanisms, payers have much more impact on the management of outpatient verses inpatient antibiotic use. And Medicare which is expected to be a major payer for limited population antibiotics is somewhat insensitive to drug price. And while pricing is a factor in reimbursement decisions for private insurers, it's only one of many considered.

So taken together, our discussions indicate that payers will not play a major role in influencing the use of limited patient antibiotics in the inpatient setting, at least not in the immediate future.

With respect to monitoring, conference participant outlined several potential systems to track the use of limited population antibiotics. Registries were suggested but high costs were a concern from the company's perspective. The FDA's sentinel reporting system was mentioned as a potential mechanism for monitoring events linked to limited population drugs.

Finally electronic health records and the CDC, NHSN antibiotic usage module were both discussed as a potential tools for tracking antibiotic usage. However, neither of those are widely adopted today. So the comments I've made here are only a fraction of what we learned at our conference. We're working to synthesize the full range of ideas that were discussed and we look forward to sharing this information with the FDA. Thank you.

RACHEL SHERMAN: Thank you for your comments. Questions?

EDWARD COX: Thanks for your comments Nicole. Just wondering, you talked about appropriate use, and getting to appropriate use, if I understood correctly, it sounds like the thinking is more that, the folks involved in stewardship activity, infection control and formulary committees might play a greater role. Did I understand correctly on that or is that what you were thinking there?

NICOLE MALONEY: we are thinking that under the current reimbursement mechanisms, and we heard from payers that it's more difficult to, kind of in advance impact the use of antibiotics in the inpatient setting. And that's because claims are done on discharge basis so unless something is re-examined, that's going to be difficult for them.

ISSAM ZINEH: one of the solutions we heard from one of the speakers is this idea of registries to be an effective mechanism to track, but we're hearing from you I think that those, at least economically would be burdensome and so was there a sentiment among attendees of the conference that is not a preferred mechanism. In other words if we go down this path and say registries are the way to go, is it likely that we'll get some sort of resistance, that registries are not a sustainable mechanism for these kind of drugs?

NICOLE MALONEY: we definitely heard that registries are expensive to set up and maintain and we heard that from I believe two out of the three companies that we had. We also heard that they are expensive for all around. However electronic health records seem like something that had more promise from the hospital perspective.

RACHEL SHERMAN: Other questions? Thank you for your comments. Since we have a couple of minutes, I was wondering if I could ask someone from Amicus, is Ms. O'Connor still here from Parkinson. So we've heard a lot this morning on antibacterial meds, those align with obviously the IDSA LPAD proposal, there's a new proposal by PCAST could be interpreted as being broader. If taken the new line of breakthrough drugs fedazio or fedazia (depending on how you pronounce it) and normally you have yet to see guidance from us on track. Does the SMU concept, do you think you can add something to breakthrough or do you feel, because remembering that as laid out, SMU to speak broadly, is the notion of targeting a narrow, perhaps more seriously ill group of a broader disease where there are less seriously ill people. So I'd be

curious if both groups that didn't represent this side of the house would comment on whether this adds something to breakthrough or not.

JOHN CROWLEY (Amicus Therapeutics): I do actually think it adds to it. I think they're complimentary and Pompe may actually give us a good example. There may be future therapy, I hope there are that are designated as breakthrough therapies in Pompe disease but then we have to think is industry, and with investigators how and where populations of Pompe disease do we apply them. I can see perhaps having a breakthrough designation for molecule and then with specific population study, may be infants, adolescents or adults in Pompe, there you can apply the SMU designation.

REBECCA O'CONNOR (Parkinson's Action Network): I agree, I think that there is a potential for complimenting here. I do think again that as has been mentioned by others, the interplay between breakthrough and other approval pathways is not entirely clear, especially for populations like ours which some don't even recognize, from the outside perspective as sub-populated and so I think that's really a role that the agency has a large role in explaining the differentiations.

RACHEL SHERMAN: Additional questions?

JOHN KIRK (Amicus Therapeutics): I was going to add that breakthrough therapy designation is a little bit different in my mind because you have to come forward with clinical data for that mechanism whereas the pathways we're discussing today is from the beginning, more from the discovery forward point of view. So I think they're very different but should be able to co-exist though.

RACHEL SHERMAN: So we reconvene at one o'clock. Enjoy your lunch.

RACHEL SHERMAN: Welcome back from lunch. Our first speaker will be Alan Solinger, from Pharmaceutical Product Development, LLC (PPD) Association of Clinical Research Organizations (ACRO).

ALAN SOLINGER: Good afternoon, my name is Alan Solinger and I'm representing PPD, the Association of Clinical Research organizations. Although I am vice president of global

therapeutic for immunology, rheumatology and global product development group at PPD, I think also, it is key that I have over 30 experiences in basic research, clinical research and large format and biotech and in the CRO industry not just PPD but several of the others. More to the point, I actively care for patients with many of the disorders to be discussed today.

PPD is a leading global contract research organization or CRO, providing comprehensive clinical research services to help biopharmaceutical clients deliver life-changing medicines to people in need. Over the past five years alone, we have conducted more than 5250 clinical trials in more than 100 countries, across the full spectrum of human diseases. PPD is one of the original members of ACRO. The Association of clinical research organizations represents the world's leading CRO's. ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO's members conduct thousands of clinical trials and provide related drug development services in more than 115 countries, while ensuring the safety of nearly 2 million research participants each year. The FDA has requested input on a set of six topics as noted in the meeting notice.

For the first one, the effectiveness of adding an additional pathway to expedite drug development, industry welcomes expedited processes. The framework of this proposed process needs to be acceptable to regulatory agencies and should ultimately make this what our patients need. This is what we should be doing. We want it to work.

The second topic, which is whether serious or life-threatening conditions need a new approval pathway, we feel this is an area that really the sponsors may have more to say. You have heard some today and you will hear more later in the afternoon. To me, as a board-certified immunologist/rheumatologist many of our illnesses have a broad spectrum of disease severity but none as broad in clinical diversity as for example systemic lupus erythematosus. The disease with subpopulations with life threatening aspects, right for targeted interventions such as renal disease, immunologic manifestations, neurologic complications, and cardiovascular manifestations. And as a side note, as an immunologist, I feel that immunology covers all diseases, we own everything and we are going to cure everything, but that is my personal editorial comment.

The next topic, whether this pathway could be particularly useful in the development of antibacterial drugs, as you have heard a great deal this morning, this is a very major issue. With

our internal in-house expertise, we feel that treating complicated infectious disease with a high rate of resistance organisms should be recognized to be similar to neglected diseases. Minimal safety databases at dose and duration expected in the label, done in a single adequate and well-controlled study is appropriate, but accomplishing this is very difficult and this is one where there needs to be a great deal of discussion with the agency, sponsors and with physicians.

We should reconsider non inferiority margins, not readily able to identify resistant organisms, prior to enrollment in patients with acute infections. The challenge to recruit adequate patients with demonstrated antibiotic failure; this would necessitate continued surveillance post approval for efficacy and safety. In addition, we need to relax restrictions on prior antibiotics, which I do not think has been mentioned earlier.

What might be the risk-benefit considerations to be taken into account regarding the smaller population, with more serious manifestations of the condition? And this I think requires across the board, not just infectious disease. More severe patients clearly have a shorter expected lifespan and that is something that we all realize in the clinical setting in spite of our advanced therapies and technologies. Subsequently there is less opportunity to see benefit. This was mentioned in earlier testimony and is a key issue. While it may show it an earlier disease, that goes counter to what we are trying to talk about today. We want to look at the serious disease, how do we differentiate those patients, how do we treat them, how do we define as for the purposes of this hearing?

By use of expanding expertise in genetic markers such as an area I worked on many years, HLA typing as far as the new therapeutic interventions and the use of proteomics, cell makers, all of these are becoming more and more an appropriate part in deciding on what our select subpopulation are to utilize. For many of the diseases you have heard about today, this actually can be somewhat easy, but for the diseases I deal with in immunology/rheumatology, up quite as clear cut and not quite as predictive of what you will see in the clinical setting with therapeutic intervention.

High-risk patients are identified earlier in their disease processes with many of these markers, and are thus population that can be evaluated best in this new proposed clinical pathway. However, the cost of research in these targeted diseases may not be proportionately lower. We all have to realize the cost may not be the reason for going into the smaller more specified

populations and sponsors, hopefully, they will testify to this more today. It may steer away from areas where the cost are high and the yield of patient number as low.

On the other hand, you have heard of ways to mitigate this. We hope this can be discussed further with many of the appropriate parties. This not really part of the CRO impact on drug development. The potential interventions needed in the proposed process are likely to make use of populations enrichments as mentioned above ago. There's a long history within the FDA of looking at enrichment rationales. This is an area that is starting to expand and be discussed more actively, but it is easier said than done, as a clinician, and someone who has done clinical trials, and now someone who also runs clinical trials. Key also will be early discussion with the agency of post Phase I delineating the Phase II plans. And I think if there is a bottom line to what I would be like to get across today, communications is key in this process. We are not going to get an answer right away from these hearing, this is a growing, living process. This is not going to be fixed and concreted any time soon or within our lifetimes.

We realize that the process for obtaining agency input especially early in the development process, has been an active discussion point in general. However, in the early delineation of the proposed new approval process, this aspect may be the key aspect in making this a viable development track, that is early definition of study populations, validation of relevance of selected markers with sufficient sample size, the possibility of using an SPA like process in these studies and early confirmation optimal doses and schedule. This is a difficult issue. Sometimes you may need to get out into the marketplace with an acceptable dose and the optimal dose may then be defined after marketing has been approved. But I think companies and the agencies will obviously need to discuss this, CRO and groups are certainly well aware of this and actively discussing with our sponsors as we go forward with plans.

CROs have been actively brainstorming innovative approaches to current issues. In our case, we currently have working groups that are evaluating bio similar drug development and also a group that is growing quite a bit in its importance to our sponsors is pediatric drug development. In addition, diseases working groups have been able to network with an ever-growing list of key opinion leaders, beyond the capabilities and long-term interest of potential single sponsor. There is also the capability, within the CRO industry, to become the intermediary in establishing consortium sponsors for various life-threatening illnesses; where innovative multidrug options may not be tenable for any single sponsor.

Use of newer aspects of data development has a place in discussions today. An example of an approach utilized in our company is that of Bayesian statistics. In summary, the discussions today have the potential to lead to earlier access of severely ill patients, to innovative therapies with the following key takeaways: Early industry regulatory, key opinion leader and academic collaborations, adaptive flexibility in agency requirements, and last of all early confirmation of the dose and schedule. We would like to thank the FDA for allowing our company and the CRO industry to have this opportunity to give some initial input in this process. Thank you.

RACHEL SHERMAN: Thank you for your comments. Questions?

ISSAM ZINEH: When we think of areas that have recently had some success in bringing new therapies to market from where conditions we think of diseases that have highly networked communities like cystic fibrosis and certain cancer areas. The CRO as consortia sponsor model seems very intriguing. Do you have any examples of that where something is up and running?

ALAN SOLINGER: I would say there are a couple of areas; one goes back to a time of the previous CRO, that time goes back into the mid 1990's, I was working at a CRO that was asked by a consortia of 17 bio pharmaceutical companies to look at doing multiple drug therapies in a developing disease called HIV. This was some of the initial work done in hard therapy. At that point, five studies were put together to look at three and four drug combinations in various, very well thought out processes. None of the companies could actually approach these on their own. The politics, the legal aspects were daunting at best. By use of a CRO, we were able to pull these studies together, get them enrolled, and get the data.

Three of the five studies I would say are a clinician, were very successful in defining their endpoints. One was equivocal and the other actually had some very poor enrollment issues and some safety issues. But overall, this was an example where some leading data very complicated areas led to some future developments that were very successful in clinical setting.

Another area that I am actually very concerned about, as I work as a rheumatologist and have been for ages, I think the area of pediatric rheumatology has been one of significant need. At the present time, there are two significant clinical consortia, one in Europe and one in the US where we have been working and I personally have been working great deal. This has made development in these areas much more tenable and it has also been able to bring in a lot key

opinions leaders to work in this process in a more generic sense as opposed to specific drug development or in the area of product use in appropriate disease.

Another one is not a CRO issue, but one in the rheumatology area, there is a group called OMRACT outcome measures in rheumatoid arthritis clinical trials. We have been able to work and I believe with at least one other CRO who are active members of this group. There're clinical endpoints, clinical trials operations have been discussed a great deal across a great number of auto-immune and inflammatory diseases in helping to set the clinical criteria that will be helpful both to industry as well as to the agencies. For that particular group, there are FDA and EMA representatives sitting on OMRACT. I have personally worked with them for approximately 10 to 20 years of existence. So those are the examples I would bring up.

RACHEL SHERMAN: Are there any other questions? Thank you for your presentation. Our next speaker is Andrew Emmett from Biotechnology Industry Organization, BIO.

ANDREW EMMETT: Good afternoon I am Andrew Emmett managing director for the Biotechnology Industry Organization, BIO. On behalf of BIO we thank the FDA for the opportunity to provide comments on the proposal to create an alternative approval pathway for certain drugs intended to address unmet medical needs which for the purpose of this statement I will refer to as the special medical use designation.

BIO appreciates the agency's ongoing efforts to identify creative approaches to speed the development of innovative new therapies to address our nation's public health priorities, particularly for the serious and life threatening conditions. BIO also thanks the President's Council for Advisors of Science and Technology for its work on promoting biomedical innovation.

BIO represents more than 1100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States. Our members are involved in the research and development of innovative healthcare and cultural, industrial and medical environments biotechnology products. BIO is currently evaluating the SMU designation concept and we're assessing several key issues to help inform the discussion. We are committed to working together with FDA and other stakeholders to articulate a potential new regulatory pathway that can successfully advance the development of new therapies for serious manifestations disease.

BIO anticipates submitting more detailed comments to the written docket to simply address the six questions proposed. The following questions represent some considerations that BIO hopes FDA and other stakeholders take into account and further dialogue regarding the proposed SMU process. First, will FDA continue to prioritize implementations of the FDASIA expedited approval pathways? Under FDASIA, Congress directed the FDA to modernize the approval pathway and to implement a new breakthrough therapy process. In light of the resource commitment of these activities, we encourage FDA to continue to prioritize the recommendations of the FDASIA approval pathways.

Second, does the FDA require additional authority to implement this pathway. As noted in the PCAST report, it is unclear as to what extent FDA's existing authorities are sufficient to implement this novel and new pathway. BIO would like to have a clear understanding of what new authorities may be necessary and how current authorities including those related to labeling restrictions and use could be applied. We know for example that FDA commonly approves therapies intended for specific subpopulations, if the product is appropriately labeled for that subpopulation. Additionally, FDA has considerably regulatory flexibility embodied under its investing authority to expedite approval programs to address serious and immediate medical needs while ensuring safety.

To advance the discussion, we encourage FDA to discuss publicly whether this pathway can be established administratively whether via regulation and guidance or whether Congress must pass legislation and the relative merits of each approach if feasible.

Third, how can this pathway be designed to balance expedited development and post – market restrictions. It is important that any pathway equally balances the dual priorities of expediting clinical development through smaller and more targeted studies, and the use of authorities that promote responsibility prescribing for specific subpopulations through appropriate labeling and instructions of use. BIO believes that any potential SMU proposal should provide clarity about the mechanisms or processes that actually expedite the clinical development of these products if it is to include post market restrictions of use.

Fourth, will only the sponsor be able to request the SMU designation and when in drug developments will designation be available? The PCAST reports states that the FDA should implement drug approval pathway under which the sponsor could propose, early in the development process, to study of drug or initial approval under designation as special medical

years. However, it is unclear from FDA's Federal Register notice if the FDA designation would be voluntary? i.e. available solely upon the sponsor's request similar to fast track of breakthrough therapies and other processes. It is BIO view that pathway should only be available at the request of the sponsor.

Additionally, it is unclear whether for the pathways to be granted early during the drug development process, like fast track and breakthrough therapies or upon the time of FDA review, like priority review. We suggest that the designation should be available early in the drug development so that the sponsor can design appropriate clinical studies for use in the pathway. For example, by conducting clinical studies based upon the most severe manifestation of the disease without having to progress first through more moderate disease populations.

Fifth, how will the subpopulations in eligibility criteria be defined? The new pathway may lend itself to certain indications characterized by specific subpopulations with a severe form of a more common condition in such as drug resistant pathogens in morbid obesity with noticeably different benefit-risk profiles. And with more restrictive labeling may facilitate the treatments for the subpopulations that would not be justified for use in the broader population.

However, it's important to develop greater clarity around how these subpopulations will be characterized. What exactly is meant by accepting a different benefit risk profile? And how would FDA and sponsors achieve a common understanding of this criterion? We also request clarification as to whether the term serious and life threatening conditions and unmet medical need would be interpreted in the same manner as the fast track statute or will either term be applied under the new FDASIA pathways.

Additionally, it is important to ensure the efforts to make more medicines available to patients suffering from the most severe forms of conditions do not hinder the development and approval of medicines for the broader patient populations. FDA must always strive for a balanced benefit risk approach when reviewing medicines for any disease including Alzheimer's, diabetes, and other chronic diseases that affects millions of patients. It is imperative that while recognizing patients suffering from the most severe forms of the condition may have a different benefit risk profile than those suffering from a less severe form of condition, any new pathway should not translate into prohibitive requirements and standards to obtain approval for a broader set of patients.

And sixth, how will this pathway be aligned with existing incentives for innovation? BIO also believes considerations should be given as to how this program would align with existing incentives, including market and data exclusivities. Given the intertwined complexities of the various incentive structures, many of which begin at the date of approval, we believe that FDA and other stakeholders should get as much clarity as possible about these issues, so that sponsors may note an SMU designation decisions that permit appropriate development and commercialization of products. We are also evaluating how this pathway may relate to rare disease drug development. Orphan drugs are already used in small patient populations and there are already concerns about the ability to enroll studies and the economic viability of rare disease drug development. And it is unclear how the SMU designation will interact with the orphan drug designation, in particular the interaction SMU proposal and the proposal published last year by the FDA regarding orphan diseased population subsets.

And finally, what will be the impact on the practice of medicine. BIO supports efforts to help healthcare providers appropriately understand and utilize the information and product labels and to better evaluate the benefit and risk profiles of different therapeutic alternatives for unmet medical needs. And SMU logo may be another tool to help inform providers and others of unique prescribing considerations. We would like to understand the impact this proposal may have on the practice of medicine.

Sponsors and FDA involvement should be kept at a minimum. Whatever limits an institution places on SMU products should not prohibit judicious prescribing by trained physicians based upon their informed judgment of what they deem to be the best treatment for an individual patient based on their unique needs and circumstances. Limits found for example on formulas and health system guidelines, should not preclude physicians from exercising sound medical judgment. FDA's current initiatives related to education, outreach, training and improved professional and patient labeling are positive ways to encourage health care providers properly understand and utilize the labels and better understand the benefit risk of unmet medical needs. These initiatives should continue to be an element of the broader conversation.

In conclusion, thank you for the opportunity to provide BIO's initial perspective on special medical use designation proposal. We look forward to engaging constructively with FDA and stakeholders as these discussions progress with the shared goals of advancing the development of

new therapies for serious and life-threatening diseases. I'll be happy to answer any questions. Thank you.

RACHEL SHERMAN: Thank you for your presentation. Any questions from the panel?

ISSAM ZINEH: If you can clarify a point. I think it was point 4, where you state BIO's position that only a sponsor could request SMU designation and so I'm going to infer that the alternative is that FDA reaches out to a sponsor and says, "We think you might have an SMU, you would be appropriate for an SMU designation? Can you clarify if that is the alternative that you mean? And if so, what would be the downside you would see to something like that?

ANDREW EMMETT: We do believe that it's imperative that the process be voluntary to the sponsor because as they are making commercial decisions about the viability of the development program and their product, they really do have the most information about these considerations about whether the SMU would make the most sense about that particular products and their business model. Of course, we are open to as much communication between the FDA and the sponsors as possible. And I think that good interactive communication during early development is going to be a critical component of this. I think it is perfectly legitimate for FDA to discuss different expedited approval options to the sponsor as a part of that communications, but it should remain the sponsor's product.

RACHEL SHERMAN: You brought up obesity and in a way that is a nice clear cut example. So, if a sponsor were to develop a product for the morbidly obese, and how do we define that; by BMI, by being a candidate for bariatric surgery, which we know carries a mortality of about 1%, and not study it in slightly heavy people, sort of speak, given our current paradigm and current regulatory authority, how would we feel comfortable that it would be used only on this morbidly obese population for whom the risks are justified and not every seventeen year old who thinks that their jeans are just a little bit too tight.

ANDREW EMMETT: Yeah, I've heard that said before. I think it is important as part of this dialogue that we really tease out some of these areas where the pathways could potentially be most effective. We've heard a lot of discussion today about antibiotics; obesity is the other commonly used example. I think we really should break out some discussions on the impact on oncology and rare diseases, to see where this makes the most sense. I think there are a number of tools that can be used under FDA's existing authorities to ensure appropriate use of the

product and the SMU logo may be another one of the tools. There are also opportunities for additional creative labeling and for provider outreach, training, and education. We really should adopt a comprehensive approach utilizing all of these existing tools for the effort. Thank you.

RACHEL SHERMAN: Any other questions? Thank you for your comments. Our next speaker is Jonathan Sackner-Bernstein, NeoStem

JONATHAN BERNSTEIN: Thank you very much. Striking the right balance between speed and protection is an incredibly difficult challenge and it's one the agency has tackled over and again mostly successfully. But of course we all know that if we're going to head down this path of getting products to market faster there needs to be an acceptance that there will be some failures. Navigating these challenges is inherently difficult but History does provide us with opportunities to learn from the past.

For example, if we go back to the early 1900s, a multitude of studies started to paint a picture that perhaps, peptic ulcer disease was due to an infectious agent; at least one contributed to the disease's severity. In the 1920s, Hofmann and colleagues were able to show that a gastric acid from a human suffering with peptic ulcer was able to induce ulcers in a guinea pig. Yet still, the field did not see this as a potential link. And up through the 50s and 60s, gastric surgery was still the therapy of choice. It started to change when Tagamet hit the market in the 1970's. Really was the 1980s when HPYLORI was hypothesized by Marshall and colleagues. But it took another decade before Tachi Yamada at the NIH conference allegedly made some bold statement that got everybody to finally buy in and eventually led to a point where in fact the community started to listen. Started to listen and started to act. I've got the slides. It is supposed to be blank. Thank you. It is supposed to be blank. Thank you.

And what this example highlights is the fact that it's important not only to make the critical observations and to listen which is the stage we're at today. But it's also going to be very important to figure out how to act. And in order to do that I think that while we're looking at many of the paradigms that affect how drugs can be evaluated and monitored for use and being respectable of course of the practice of medicine, none of those approaches can be optimally tested, or implemented nor deliver their benefits if there is not enough opportunity to test them. What we're faced with is the situations where if we do not look at the picket that feeds this

pathway, that feeds the hose, it won't matter how big that hose is or how great the sprayer is that the gardener is holding.

What I'm going to do today is pose a challenge, different vision, looking further up the pathway and really focusing on how we need to get more products into the clinic for clinical testing in order to have an opportunity to test this pathway, breakthrough pathways subpart H, subpart E and all the other tools that the FDA has at its disposal.

This is another way classically that the problem is presented. We've got a lot of stuff at the beginning but little of it gets to market. And part of the reason for that is we're not very good at understanding how to pick our compounds, how to pick our therapies. If we look back at the literature, we can see many examples that at first glance give the impression that our approach for selecting products is pretty good. This is one. It is over a decade old and shows that in a series of compounds, 70% of the time the animal toxicity correlated with what was seen in the clinic. And you can see some breakdowns by different species. What is critical here to understand is this is only half of the equation, because many products are removed from the development pipeline because of what's seen early and we don't even know whether those early signs will translate into clinical effects in people.

So the problem with preclinical testing is we end up with essentially some false positives, false negative and end up with giving whole landscape one of false hopes, because we can't pick well from animal tests. Certainly not well enough to have the impact on the unmet public health needs that we're focused on today.

The key thing here about PCAST is that it does focus on many of the parameters across the development pathway. I think for the most part we have interpreted in today's agenda as being one where focuses primarily on what's happening in a drug evaluation and utilization late in the process and postmark opportunities are very important. For example, it gets at payment and the role of CMS and that's important. It doesn't go to the whole economic issue of how we're going to face rising costs in our healthcare system and whether things such as a cost effectiveness claim would be an important part of an FDA approval process. We all know one gets what one measures, one gets what one lays out as an incentive. If we want to control cost without reducing quality, that might be a mechanism.

And anybody who has been involved with the performance of clinical trials knows that process needs to be made more efficient as was touched on in the PCAST report. We all know the importance of IRBs. They protect the patients, protect the science but when you do a trial with something going out against a new target or using a novel approach, what you find consistently is the IRB system is one that serves as a very mighty barrier. And I think that most people who develop drugs know that barrier is as great as any other barrier in that early stage of drug development. So these deserve some attentions as well. But what I'd like to do again is bring you back to this idea of a picket. What are we going to do to get more products into the clinic? Without that, none of those programs can be tested as well as optimized as well as we need them to be and our ability to impact public health is going to be limited as well.

So to do so, what I'd like to do is quickly just go back in history to another lesson. We're all familiar with the story of how vaccines came to be; some of us more than others. Back in the 1700s across Asia, Variolation was used. Those of you who don't know how it started basically is the idea that you take dry scabs from people infected with small pox, create a powder and have others inhale it in order to prevent themselves from getting sick. This is an example of how one has to do a risk benefit calculation. Variolation killed 1 to 2% of the people. Spontaneous small pox killed 30%. So when it was first recognized, the Ottoman empire brought it back to Europe. There was a rapid uptake, people started to listen. Germany developed the first vaccine, since it was derived from cowpox, it is called vaccination from the Latin meaning cow. And by 1977 the last case was reported.

This is an example where people listened and people acted. What I'd like to do is propose a specific set of steps the FDA consider taking on. The proposal gets down to gets down to shifting the burden. So as we're asking for science and data to allow a product to be established as safe and effective, so too should we demand and expect and share the science that justifies the preclinical testing that is used as a requirement for getting it to the clinic. The FDA should evaluate these preclinical tests invented largely on the small molecular and only require those that are demonstrated based on scientific evidence that have predicative power. Therefore, more products can get into the clinic.

This may sound like it's a very risky approach. People are going to be very uncomfortable moving away from tradition, I understand that. One has to figure out how to mitigate the risks. And you've already identified the first component which is to identify unmet public health

needs. And the other I would suggest is that we select narrow areas for our pilot program. And the way to do that is to pick a handful of areas and I've discussed these with a variety of people involved in medical product development. You'll see that 4 out of 5 relate to cedar regulated products. These are products for which the standard preclinical test models for small molecules just don't have basis published to say they must be done. And therefore they run the risk of killing off products that could really address unmet needs as well as allowing us to make decisions that end up hurting people in clinical trials.

If we focus on advanced disease for unmet needs, establish the appropriate risk benefit criteria, establish an effective communication process so the patients know what they are getting into; at minimum what we provide patients is hope, that they have a therapy that may actually affect an important condition.

So it maybe a question how we go about doing it. I mentioned before Variolation to vaccination is in the step to where we get to action. There were other examples as well. I think it's a three stage process. We've done the first two. It's time to act. Looking back in history, there were even recent examples that tell us that we have a road map. That road map can be exemplified by the HIV crisis where we align political force with scientific muscle and got to a really terrific transformation and what happened to people. Thank you.

RACHEL SHERMAN: Thank you for your comments. Questions?

ISSAM ZINEH: Thanks for the presentation. Do you see an unintended consequence to be a shifting of burden to early phase clinical trials in terms of very safety monitoring? If you don't have an estimate of what the safety problems will be going into the clinic, you might as a matter of comfort require a whole battery of human testing from a safety stand point and that might defeat the purpose in terms of efficiency of early phase trial designs.

JONATHAN BERNSTEIN: I think that, in any change, any shift of paradigm, there is always risks. And that's a nice one because that's foreseeable. There are going to be unintended consequences that we can't foresee till we're there. That's why I said at the beginning that if we're going to look to transform, we have to realize there are going to be failures. That particular one I can tell you from doing human trials that the amount of safety testing when you are starting out should be very intensive. And maybe it will limit the amount of patients that are willing to enroll, that's certainly a possibility and that's why I say pilot manner.

We say under the authorities that you could do this. In these areas of specific technologies that are unlikely to be predicted by clinical test, pick an area that someone has not chance. Pick somebody with inoperable pancreatic cancer. Find those areas where there are no alternatives. Work really hard to communicate that uncertainty. And then move forward. Because that is the only way we are going to make progress is to try some experiments.

RICHARD KLEIN: You mentioned the IRB being a mighty barrier and I'm wondering if this paradigm were to shift this was do you see the IRBs not being a major barrier to that kind of model?

JONATHAN BERNSTEIN: I think the IRBs would be their very nature how they act now would probably become even more of a barrier. And that has to be addressed. IRBs in early trials or innovative trials come across most frequently as the protector of institutional lie ability, so there has to be at some point an idea that maybe it's an organization like the office of human resource protection that has to step up and say our role about protecting patients in research also means, we have to protect their right to engage in research and we need to reach out proactively to IRB's to explain why this is important, and to engage with them early on. If the FDA decided this pilot would be worthwhile, that the FDA would probably be doing great service by organizing a call with the IRB and explaining why the FDA believes this makes sense.

RACHEL SHERMAN: Other questions?

I have one. I would refine your last slide slightly and say scientifically savvy political force. What do we do where we don't have a scientifically savvy political force?

JONATHAN BERNSTEIN: Seems like the political force sometimes is going in the opposite direction in many of the times where we look at it. And that was a particularly wonderful alignment of very well thought out and executed political force. I think what we have to do is enlist people and try to encourage them to stick out their neck two. And we saw today there are people from the Parkinson's association. If we can enlist them and give them hope that by going in this direction, there's something to get, then I think you have an option of enlisting that partner. So I just say to a potential partner, stick your neck out and maybe we'll do something with you. But if one leads, then other will come. Maybe the political leadership ends up coming from the FDA.

RACHEL SHERMAN: Thank you for your comments.

ISSAM ZINEH: Can I ask one more quick question?

RACHEL SHERMAN: Of course.

Your model is intended to get more compounds into testing. And does it default to sort of the standard battery of clinical tests at that point? Is it standard drug development from the point on?

JONATHAN BERNSTEIN: Well, I think that could certainly be. It could be feed into a variety of programs that you have already in existence. So it could go right into standard testing. I think it's a function of the compound and the indication and how confident people can be that the risks can be managed. The clinic is where you are going to get the information, where it tells you whether it's going to work or not, not the animals.

RACHEL SHERMAN: Thank you for your comments and a shame less plug. FDA is a big proponent through our clinical trial modernization through our clinical trial transformation initiative.

Our next speakers are Sally Okun and David Clifford from patients like me.

DAVID CLIFFORD: I, I'm David Clifford from Patients like me. Unfortunately Sally is not here because her plane was delayed coming in. We're going to spend time today talking about what patients like me is and then answer one or two of the questions that were asked of participants today.

So today the title of our topic is on pathways; the Roles of Patients, Pharmacovigilance, Phenotypes, and Prediction. So what is patients like me? It's a website you can go to if you have a chronic illness, where you create a patient profile, share with people like you, find support and compare experiences etcetera. This is what you would use if for as a user. What else is it? It is a platform for spontaneous reporting of information from people who use drugs and devices but mostly drugs. We use the information to inform clinical research, non-profits, pharmaceutical industries. We do some work sponsored by government at this point, we do work with major other research non-profits but mostly with the pharmaceutical industry.

And we help people answer this question, which is relevant to the panel today. Which is given my status, what's the best outcome I can hope to achieve and how do I get there? So we're going to be talking a little bit today about some of these risk benefit questions we have.

Here's what a patient profile looks like so you get an idea what sort of data we collect. So we've got patient report outcomes. Quality of life score which corresponds to the SF 36 and we also monitor what treatments they take using a gantt chart. So if there's dosage switching there as there is in the third area down, all of the text is very small and I apologize for that, the bar gets thicker as the person changes dosages. And you can track that, sort of at a glance against clinical outcomes.

And then we have a non-mild moderate severe symptom criteria, as well as it seems a lot of patients indicate side effects of drugs they might be taking. This is a lot of data designed by engineers to help people with amyotrophic lateral sclerosis, determine what other people with that disease have done. There is a lot of well-structured information out there that's consumer friendly. And you are generally putting in the information seeking when you are diagnosed with ALS, and to allow people to contribute to a legacy of research after they have struggled with disease overtime.

So one of the questions I was asked was what approaches could be undertaken to prevent, manage or use of off label drugs in a broader population where safety and efficacy has not been demonstrated. I mentioned that we have this ALS data collected over time. One thing we were able to do with this was observe the effects of patients who were experimenting with lithium in treating their ALS experimenting using a chemical compound off label to determine whether they had any benefit. There's a paper that came out, a publication that indicated that lithium delayed the onset of ALS.

We had tremendous amount of data of people's ALS scores which was the outcome these scientist say was modified. And we had a few hundred people on our website decide they were going to start using this off label drug to delay the onset of ALS. Because you'll do that if you have ALS.

So we were able to anchor the reported data of the patients from prior to the point they had started lithium and compare the trajectories of their needs against one another. So it's a projected outcome and projected longitudinal presentation of the disease overtime that's fairly linear. And we were able to compare the expected FRSs against the observations that are being made in the system and able to determine that lithium in fact had no effect on patients in the wild when used and reported on through our platform.

So this is an interesting finding. Patients can report on their data, based on their understanding of what a drug does outside of a trial environment. So similarly, there's this great thing that's being put together called mini sentinel, it has a current data model of HRS in billing records for use for secondary use, safety, efficacy, power of data, impact of label changes on outcomes generated from clinical encounters, drug uses and amounts, ICD 9 codes or ICD 10 codes where they are used and hospitalizations. But there's some challenge. ICD 9 coding frequently has errors. There's inability to create linkages between the drugs that patients are on and the code or the reason for their visit.

On the other hand there's the data we generate which is complimentary. Patients in this is, just an example of a model, for data collection outside of the clinical system. It's been built somewhere. So it's a complimentary data set showing causations between drug and side effects. They could be wrong. But it's their observation and it is some data which is better than nothing. They measure drug efficacy outside of the clinical encounter, meaningful for diseases where the scales exist so you do not just have an ICD 9 code or you just don't have a lab value but you have some patient reported outcome scale. But there's some lower truth standard; it's not clinical data. And the reliability of this report has been minimally tested and we do have a health data integrity team which works full time to ensure data quality and will offer tools to the patient to allow them to complete forms more accurately. But it is not 100% solution. But it does lead to interesting findings like this.

This is the clinical trial data for Pregabalin, Gabapentin and Duloxetine; three drugs that are used to treat Fibromyalgia. All of them caused incident weight gain in some percentage of the sub populations of the trials. Incident weight gain with fibromyalgia causes increased pathology of the disease. Our evaluations which come from people from the quote, unquote, real world indicate much higher levels of incident weight gain, observed in the trials which is problematic. And we measure these things for a longer period of time than required in trial reporting. So this is another thing that talks about, you can look at outcomes data from the real world that's reported and use that to inform indications or efficacy of drugs separately.

One of the questions about what approaches approved under this pathway to determine whether or not being used consistent with terms of approval. We've done quite a bit of work with off label drugs. That's one area you can look at a comparison. If you say okay we're going to test this for safety, test this efficacy. There's a tremendous number of off label drugs for the safety

and efficacy have been tested but used in another disease. 2,000 unique PROs modafinil across 5 conditions found that less than 1% were taking it for approved purposes. The primary use of amitriptyline is to dry excess saliva which is using it for the side effect of the drug. So similarly I think we can look at the way clinicians and patients are using drugs off label to inform some of the things we're considering ethically under the FDA pathway questions.

This is about patient centricity. So there's work for the FDA now talking about how patient centricity should be used to define end points. Serious of life threatening conditions what needs to be taken into account before and after marketing and how should they be addressed?

Heterogeneity of treatment affects is an issue here. Patients may receive treatments that have no benefit or worse cause harm. Patients may not be receiving treatments that could benefit them and failure to recognize THE can lead to suboptimal outcomes. So this is little bit about patient centricity and scales. There's something called ALSFRX, so if you have an ALSFRX of 0 which is the scale used to approve drugs, again, you can be alive, and highly intact. There could be drugs that could be modifying people's outcomes when they have an ALSFRX of 0 and we don't know about them because there's no scale to approve them on. Multiple sclerosis rating scale; it doesn't provide a granular measure of disease for many patients using it to monitor their disease. Part of this is because of the classification of multiple sclerosis, it's kind of a bucket disease. So there are a lot of different pathological indications that can present as something that we call multiple sclerosis. So some of the issues on efficacy, scales need to be specific and stable and can be co-developed with patients to get better measure of diseases in a way that matter to them so we can present drugs that are more meaningful to patients.

Some of these questions about how do we determine a sub-population? Generally it's through observation and diagnostic criteria; Paxomia's release was formulated through a consensus process and rarely through a biomarker. Many of the challenges with patients with neurological disease have to do with the coding of the symptoms and names. So for example, if you have epilepsy, what does it mean? It means you have seizures. More granular than what we're looking at stricter, and stricter exclusion criteria in order to test or approve a new drug, which can be problematic.

Part of the method to get a more expedited pathway is better for disease so we know when we're approving drugs what we're approving those drugs or assessing those drugs for. An example of this is a patient who presented to a physician indicated our doctor visit to track found they had

bipolar disease whereas their clinician noted major depression because when they grasped their symptoms over time, it was side swindle. I noticed the blinking light so I assume that means I should wrap up.

So this is systems biology, we evaluate diseases area by area. But these things are highly interactive, highly coincident. This is just the way diseases work. This is a new method for evaluating these diseases; looking at patient phenotype and genotype in a circular model which you can't see on this around set of arrows in the back in a light shade of blue. That is all I have. Slides are submitted for your comment.

RACHEL SHERMAN: Thank you for your comments. Questions?

EDWARD COX: If I understand things correctly. All the information entered is from patients?

DAVID CLIFFORD: That's correct. Currently all the information is entered from patients. We're doing a pilot with a integrated care provider looking at how patient reported outcomes can be used in care processes to inform the process of care.

EDWARD COX: How many patient records in essence do you have within the database? I'm just curious to get the idea of the magnitude of the size not an exact number.

DAVID CLIFFORD: Around 180,000 with over 1,000 different conditions. Our large largest population is Fibromyalgia and there are 30,000 patients and our second largest is multiple sclerosis and there are about 3000 patients there. These are significant populations.

EDWARD COX: And then you're sort of getting to my last question which is are there certain diseases, conditions or is it limited to certain types of disease conditions? Or from your experience, are there certain types of disease conditions that are most amendable to the approach you're using as compared to others?

DAVID CLIFFORD: Right. One of the reasons I was talking about neurological conditions of complex ideology or dire presentation, those are the diseases that we found people are most information seeking. So when you have something like Parkinson's or multiple sclerosis or fibromyalgia and you go to your doctor and you say what does this disease do and the doctor says I don't know or kind of this or you should be able to expect sort of that, these are areas where patients tend to seek out additional information. So neurological conditions primarily.

ISSAM ZINEH: There's a pretty good literature that suggest the frequency of adverse event reporting driven by how much counseling you provide a patient. One of the questions I would have for a mechanism like this is, it would probably seem pretty good to capture on the risk side adverse events we know about so that patients would capture that report. The use of this kind of model for a therapy for which the exact risks are not really known, I wonder if you can comment on that. Is there some ability of this network to be able to capture adverse events that had not been previously reported in literature or the label? Do you have examples of that?

DAVID CLIFFORD: We have filled out and done number of adverse event report forms. One of the rules not sure is this is answering your questions. One of the roles of our health and integrity team is, when they see something that is an adverse event report in the community forum or as a side effect for a drug, they will fill out adverse event report, file it for especially in cases where we have a relationship with client whose drug is on our platform and being rated on our platform by a user.

So that information is filed out appropriately now and sent in to the FDA now. I don't know what it's done with it. And one of the troubling things is many people who comment on things on the internet are people who are not happy, who are displeased with their current course or displeased with current regimen. So if we were to open the flood gates on this, then we're creating a problem for regulators in terms of the squeaky wheels of the world. Which is good to know about and useful and informative but it's a lot of data.

RACHEL SHERMAN: Any other questions? Thank you for the presentations.

Our next speaker is Roslyn B Mannon American Society of Transplantation (AST), University of Alabama.

ROSLYN MANNON: Thank you Dr. Sherman and panelist, ladies and gentlemen. I appreciate the opportunity to speak today on behalf of the American Society of Transplantation. We represent over 3000 medical professionals in solid organ transplantation and are dedicated to improve the outcomes of our patients through research, education, advocacy and organ donation. Many of the prior speakers have succinctly and or directly presented their views to questions 1 through 6 but my presentation today, will highlight what we believe is the need to consider solid organ transplantation therapeutics in this area.

I have to make the acknowledgement that I am also a federal employee and Alabama state employee and the opinions expressed today reflect are those of the ASG. The waiting list for transplantation continues to grow dramatically, these are actually out of date data, there are now 117,000 individuals listed this morning waiting for organs. The largest group is clearly the kidney and liver populations. Kidney is now about 75,000 liver about 20, and smaller numbers in heart, lung and intestine. And unfortunately the rate of transplant is far smaller than the rate of listing for transplantation; really only a fraction, less than 25% of individuals waiting on the list each year actually do get transplanted. This leads to very long and lengthy waits on the transplant waiting list.

Associated with the waiting list time is significant risk of death. Shown here are data from the kidney transplant where there is available renal replacement therapy. The mean death rate last year was estimated 6.2 deaths per patient years the peak in one particular geographic area with close to 10. The major contributors to this risk of death are older age, as you can see on the left panel and the primary disease underlying it being diabetes, this really magnifying the death rates while on dialysis.

In addition we also have a significant issue with recipient mortality despite our efforts the adjusted probability of death is about 34% at five years post-transplant and estimate about 57% at 10 years and those are recent scientific Registry data. And I provide those as you can compare it to death the probability of death at five years to things like regional spread of melanoma, renal stems and colon cancer. I think our graft survivals are much better in the past 30 to 50 years but still not optimal but we have really had a minimal improvement in graft attrition rate after the first year post transplant which I will show graphically on the next slide, not to highlight too much data that is the red, green and blue bars which remain relatively static.

And also about 35 almost a third of our graphs from deceased donors, this is a kidney, lost about five years post-transplant per month those individuals that recycle back and get replaced on the waiting list have a 78% increased risk in death when you compare those individuals who have not had a transplant and awaiting transplantation.

Another critical unmet need is if patients do well in the first five years there is a significant loss at ten years post transplantation of both not only recipient but also graft failure and this is across all solid organs. And there are a number of reasons for this and I will go into shortly. Shown here are trends in immunosuppression therapy particularly in kidney on the left upper panel, the vast

majority of patients in the United States receiving T-cell depletion induction therapy. This drug is being used in off label status, currently not labeled for induction. And the vast majorities are maintained shown on the left under Tacrolimus and Mycophenolic therapy. The major trend we see in the bottom panel is that a number of centers, a fair significant number more than 40% now are moving to steroid free regimens so the average patient in the US after kidney will only be on dual agents Tacrolimus and Mycophenolic .

We have significant unmet need and the cellular rejection rates are probably the lowest seen in the years within the first six months and one year post transplantation. In all organs we are seeing resurgent or identification recognition of late cellular rejection which may be a significant contributor to late graft failure. We also have significant challenges in the field with the ability of immunosuppression to weigh the balance between rejection verses infection because we don't really have defined assay to insure sufficiency of immunosuppression than we have drugs that have level dosing.

We have issues managing the increased risk of cardiovascular disease in patient populations, promoting patient as well as physician adherence I might add, and then the potential nephrotoxicity of the use of calcineurin inhibitors that is a question mark because it is a bit of a controversial area right now. There are a variety of syndromes and late graft failure shown here in the kidney for IFT, the heart and lung. We have significant unmet needs particularly therapeutic targets and biomarkers. There's been a lot of research in this area but from a clinical perspective, I only know of one agent which was going to get into Phase I/II trial and it was eventually halted because of the difficulties in designing the trial and defining appropriate endpoint in a specific population.

Another critical need in this field is antibody injury it is now clear both a cute, not so much acute but late injury is related to antibody, and also there are a lot of attempts to remove donor specific antibody that might advocate the opportunity for transplantation, for those patients at high immunological risk. We really need effective agents to block production, to move the offending cells without deleting the ability to make antibody.

There are a number of centers specific approaches being tried in very small trials including plasmapheresis, IVIg, anti-CD20 , antibodies some other anti-B cell agents you are familiar with, lupus, bortezomib and anti-C5 antibody. But these are not really moving forward quickly enough to identify the appropriate strategy long-term.

BK polymer viruses another considerable unmet need in the kidney patient population, leads to about 10% to 15% of graft loss despite the fact that we are better at monitoring using viral PCR there are currently no FDA approved agent on the market, although a variety of centers have a variety of strategies that they use in an off label setting.

There are a lot of immunological barriers that are out there, and I not only provide these not to make the field sound like there is a lot of things that are unusual, but that I see things down the road particularly the role of T-cell memory, the impact of homeostatic preparation after depletion and the ability to harness regulatory T cells, and these are moving to very quickly through preclinical models and there are actually a couple of centers through ITN and NIH looking at these trials to move into humans.

I also want to put out there immune injury is now recognized as a critical reactor with adaptive immunity, and we will need, soon, to look at clinical studies and man based on preclinical data. One problem that the field is really facing us is the lack of limited organ donor supply. I don't ask you to do anything about that other than everybody in this room should be signed on as an organ donor. But desensitization of donor specific antibodies in both living and incompatible recipients as well as the list of candidates has been a strategy that a number of centers including our own have utilized and this can also be paired up with kidney donation, as was reported in the recent Kevin Sacks article this past year. Again, as transplanters we do go out on a limb in order to expand the donor population. We have been looking at extended criteria donors, donation after cardiac donors and CDC high-risk donors. We accept the risk as transplant and we appropriately consent patients to recognize the risk. So that not everybody we know—the kidneys we know, at least in the first two instances may not have same short and long-term outcome, but if you look at death data, unfortunately this doesn't transmit well there be look at the left panel relative risk of one of the relative risk of death if you stay on dialysis. There is actually a trend favoring extended criteria donor transplantation if you compare to the waiting list is opportunity particularly patients with diabetes. There are highly sensitized and those having poor dialysis courses running a transplant access.

Discard rates and biomarkers is another area but I won't get into that but optimizing the functionality impaired organ is a big area of need now and a number of groups are looking at devices and solutions for what I called reanimation as well as reversal of perfusion injury. These things will be needed to move forward over the next couple of years. I also hear at previous

speaker talking about stem cells but this isn't science fiction. There are a lot of interesting preclinical models albeit not yet in primates looking at cellutis graphs certainly Xeno transplantation is back. The field will need a pathway for the study and approval of use in humans which obviously would cross a number of FDA divisions. I think the most significant issue that I like today is that the transplant immunosuppression pipeline is extremely small right now and our FDA endpoints meeting hosted by the division of transplantation, a number of issues were brought up.

Certainly I don't think anyone here today can help me with the academic geography but certainly issues in trial design were pointed to particularly, we can no longer really show that are one-year outcomes expect in a non-inferiority trial. And certainly, we have significant risk and we have shown in Phase III studies we don't make the primary endpoint in the non-inferiority studies. And there has really been no support from industry or colleagues to look at biomarkers will receive either success or failure in these trials. The industry itself is really at a standstill in transplantation because the estimated net present value is deemed too low. Trials are costly, results are unpredictable and I see the whole field shifting towards autoimmune diseases where the patient is often not fatally ill. The cost of the new drug isn't as guaranteed as it used to be perhaps, there is a steep learning curve and as already pointed out, some of the extra regulatory pressures that are provided both federally as well as locally.

So AST does recommend the consideration of trials to include requirements for markers of efficacy, but interestingly at the endpoints meeting it was a strong support for accelerated review of surrogate endpoints using subpart H as approval and the opportunity to potentially have superiority trials, for these new agents in specific areas. We recently had a very successful meeting with the generics division and this demonstrates our collegiality and interest in working with FDA. Transplantation provides life sparing therapy and organ failure immunosuppression has clearly made significant improvements over 50 years. As I have shown you there have been significant unmet needs in the field including improving long-term morbidity and mortality in our patient and the pipeline of their P is really at a standstill because of issues of cost and risk in trial design, using the usual and what I would say was outdated strategies of trial design over the last two decades. Thank you

RACHEL SHERMAN: Thank you for your comments. Questions? Thank you. Our next speaker is James Healy, from National Venture Capital Association.

JAMES HEALY: Thank you very much. My name is James Healy, physician scientist, immunologist by training, as my children often remind me. I may be a doctor but I'm not a real doctor because I no longer practice medicine. I am a venture capitalist by vocation and the president and managing partner of Sofinnova Ventures, one of the larger dedicated biotechnology investors of venture capital funds here in the United States. I have been personally involved with as an investor and board member of eight companies that have received approval by either the FDA or EMA to market their products, three in the past seven months.

I am here speaking on behalf of the NVCA and medic coalition. The venture industry broadly speaking is responsible for over 12 million jobs here in the US and we have over 400 member firms and a focus on innovation medic coalition in particular medical, biotechnology and med tech innovation. To set the stage for my comments today, I really view it at this point in time when industry is at a juncture. As Charles Dickens once said, it is the best of times and it is the worst of times. It is the best of times for innovation, because if one looks at citation indices, patent filings or the number of important discoveries, that they are all time highs. On the other hand, if one looks the number of early-stage drugs that are being developed, as the data I will share later in the presentation will document, that those have decreased significantly over the past several years. So, we have also seen a significant drop in the number of first time finds for biotechnology or medical technology companies trying to develop those projects. So as a result, this will create or may create a very significant problem that will impact the overall health of the US healthcare system and our population.

So, venture capital as an industry has focused since the early 70s on helping create and fund and fuel the biotechnology and med tech industries. Venture capital is one of the few sources of funding for early stage products. There are many data sources that document, demonstrate that most revolutionary medical innovations come from small venture backed companies. If one looks at the leading top 10 products out of the leading multinational pharmaceutical companies anywhere from 50% to 70% of the products were either discovered or the early development of the products was done by venture capital funded companies. So most of the revolution and the revolutionary innovation effects come from these companies.

If one looks at 2011, 85% of the drugs that were fast tracked drugs approved during this timeframe were venture backed. This will include products like Adcetris at Seattle Genetics for Hodgkin lymphoma which was a company we helped start and create two important products that were developed like Jakafi for myelofibrosis, at Insight Corporation or Zelboraf which the current sponsor is Genetech which was originally discovered at flexicon another venture backed company. So in the past seven months our firm has seen 3 products get approved with Vascepa, Amarin for the treatment of patients with very high triglycerides, Clobex for the treatment of patients with ADHD or Evista which was approved last week for control of pneumonia in patients with urea cycle disorders.

So, looking first at the pharmaceutical market, you can see there's been significant decrease in return on investment for large pharmaceutical companies. Where they have seen a 60% to 70% decrease in the return on capital that they have put into funding research and discovery such that current return rates it may be better off putting their money into T bills. One can also see a commensurate increase in the aggregate cost or expenditures pre NME that has been approved from roughly \$1 billion in the early '90s to approaching \$6 billion so nearly a 5X increase in expenditures and cost for product approval.

So that sets the stage for how the environment most large pharmaceutical companies live in. I would like to shift and focus on the venture capital market and emerging life sciences and biotechnology companies. This schematic is simply to demonstrate innovation consistent, we are often asked how venture capital works, how it fits in society and financing new drugs? As a firm and as an industry, we receive the majority of our capital large state pension funds, and endowments or teacher retirement systems that would include the state of Oregon, state of California, Massachusetts, Illinois, Texas and others. They give capital to us with the expectation that we will be able to generate superior returns to the returns they can see other asset classes.

As a venture fund, we then help identify promising discoveries, partner with entrepreneurs and scientists, establish new life science companies that their success is predicated upon being able to deliver innovative therapeutics in less time, less capital through collaboration with the FDA. And then at the end, as those companies are successful and the products are approved, the patients themselves can gain access to new, innovative therapies and they then contribute to benefit from the pension funds themselves. So to look at the lifecycle of a biotechnology

company, there was a continuum where the capital may be raised from angel investors. Early stage venture capital firms would put money into a series A or series B financing and later stage funds such as ourselves about focus on late stage drug development will finance series B, C, D to try and get products to market. And I think the underlying theme for each day the development is that the clinical progress is required in order to catalyze financing.

Unfortunately, over the past six years, we've seen a significant decrease of over 50% of the number of these companies looking at first time financing. During the time period from 2006 to 2012, either a medical device company on the top or biotechnology on the bottom, the number of first time finances that have been able to be successfully closed has been cut in half. That is most likely directly attributable to several facts.

First, is that the timelines have increased significantly so looking at the time from first investment through an acquisition, so M & A or biotech company it has increased from three years to four years in 2000 to over six years currently, the time it takes from first investment through an IPO is now approaching eight years for a biotechnology company. The cost has also increased as well. That the average cost has increased from roughly \$10 million to currently in excess of \$60 million or \$70 million for companies going public anywhere from \$60 million or \$150 million. So it's the increase in time and cost that causes significant decrease in the number for first time financing. As we can see here from the most recent survey from MoneyTree, collaboration between the National Venture Capital Association and PriceWaterhouse, the number of new life science companies that were funded in 2012 is at the lowest level since 1996. So we see a significant decrease year-over-year during that time frame.

Importantly, if one looks on the right and also see that the number of either Phase 1, Phase II, or Phase III products has been cut in half from 2006 through 2010. So less innovation, fewer products being developed, fewer companies being funded which ultimately will mean fewer products will be brought to market. So the problem as we've stated is that with a 50% reduction in the number of new companies and with anywhere from 50% to 70% of the approved products coming from those companies, we could see a 30% to 40% decrease in the number of innovative products that are brought to market in the coming decade.

So, the solution to that problem that we would like to put forward would be to try and work on an alternate approval pathway in particular for diseases with high unmet medical need. The goal would be to try and improve the research, discovery and development of novel therapeutics, to

do it in a way that reduces risks to patients and the companies that are developing those drugs. It also ends up importantly, encouraging the new funding of disease areas currently viewed as too risky or too costly such as many metabolic diseases that were discussed earlier today.

These are just examples of a couple of therapeutic areas that we think could be of importance. There have been a number of individuals today who talked about anti-infective segment so we will not address that. Reduce the important opportunities trying to use surrogate endpoints for CNS diseases or inflammatory fibrotic diseases and also trying to focus on small targeted patient populations in particular within diabetes or obesity as being important areas to try and focus on and collaborate with the FDA.

Our goal and next steps would be to try and participate in an open dialogue with all stakeholders to try and promote innovation, discovery, development and approval of novel, innovative therapeutics. And the NVCA appreciates the FDA's efforts and interest in entertaining that dialogue. Thank you.

RACHEL SHERMAN: Thank you for your comments. Questions?

EDWARD COX: Thanks Dr. Healy. I am just curious if you might comment, we think about streamlined development programs, you think about a more limited patient population that might ultimately receive the drug I wondered if that's something you thought about any comments you might have in a particular issue?

JAMES HEALY: It is. So as an investor, it is our primary objective to try and shorten the timelines, reduce the risk and reduce the cost. Knowing that if we are getting drugs approved for a more limited patient population, it means the commercial potential may be smaller as well. You think that's a favorable trade off, so we'd much prefer to focus on patients with high need in targeted patient populations.

ISSAM ZINEH: So when you look at some of the solutions you propose that come in buckets, into a couple of categories one is enriched patient populations' using biomarkers or a variety of designs that we devoted some thinking to. The other variable is the development of surrogate endpoints, which is a huge challenge, of course. So if that were left to the agency to do, that would be a tough thing honestly, because the community would have to, I guess, that in some

way meaningful end points, to help us do a meaningful endpoints for drug approval. So has there been any thought on how you might invest in development of novel endpoints for regulatory decision-making or qualification of new biomarkers.

JAMES HEALY: No, I think that's a very important topic. It is a large, multifaceted and complicated issue. I think our goal would be to try and invite and hope that all constituents would be able to sit at the table and try and focus on endpoints that could be validated in different ways. I think one of the things that is interesting is that if one looks at Alzheimer's disease for example, it's a very high unmet medical need, very long time frames at least within most patient populations. And challenging to know exactly what surrogates would correlate with outcomes. If there would be ways, for example, to pull data from the placebo arms of trials across the industry. It may help us all become much smarter when it comes to how understanding the disease, disease progression and correlation with different types of employees. So that is an example of a paradigm that could be used.

RACHEL SHERMAN: Just one question. Some of your more depressing slides refer to biotech and devices as well as Biologics. Are the trends the same for the small molecular components of your business? Or do you not work on that so much?

JAMES HEALY: We do for, actually with our definition include small molecules with biotech operationally but to address the question more directly, as an investor we do look more favorably on Biologics because they have about three-time higher success rate across the entire development spectrum and by and large tend to be very safe. So those would be prioritized as we look at screening different opportunities.

RACHEL SHERMAN: Just out of curiosity will the same be proved for bio-similars? Or is that an area—

JAMES HEALY: I would love to understand the FDAs position on bio-similars better.

RACHEL SHERMAN: Ouch.

JAMES HEALY: No ouch intended. That was just waiting with baited breath.

RACHEL SHERMAN: We have four draft guidance is out...we are a couple minutes ahead so in an interest of giving—getting everyone out here in time, let's take a 15 minute break and resume at 2:40 instead of 2:44. Thank you.

RACHEL SHERMAN: If everyone can take their seats please our next speaker is Anthony Castaldo. Hereditary Angioedema Association.

ANTHONY CASTALDO: I can certainly start up with some good news, that is that my remarks will be mercifully brief, hopefully cogent but certainly brief. My name is Anthony Castaldo, I am president of United States Hereditary Angioedema Association which is a nonprofit advocacy and research organization with 4300 members. we are founded and staffed by patient and patient caregivers. I would like to start by commending the FDA for holding this hearing and taking a serious look at exercising prudent regulatory flexibility by considering an alternative approval pathway for drugs that can address unmet medical needs.

Little bit about our disease, hereditary angioedema is a debilitating and potentially fatal genetic disorder characterized by episodes of swelling in various body parts including hands, face, feet and airway. In addition, our patients often have bouts of excruciating abdominal pain, nausea and vomiting that is caused by swelling in the abdominal viscera. Airway swelling is particularly dangerous and can lead to death by asphyxiation. The United States Hereditary Angioedema Association leads a nationwide advocacy movement that focuses on increasing HAE awareness and education and empowering patient access to therapy and fostering research, ground breaking research as a matter of fact, that includes searching for a cure.

Now I am appearing before you today, to not only support and endorse the notion of creating an alternative regulatory pathway for addressing unmet medical needs, but also perhaps a little creative in providing a concrete example of how this concept could be applied. For most HAE patients, a deficiency in the plasma protein C 1 inhibitor is the clear pathophysiological basis for their swelling and therapies available to prevent and treat attacks. There is however a subpopulation of our membership that have hereditary angioedema, but their C 1 inhibitor levels are normal and as of yet the pathogenesis of their disease is unknown.

Patients suffering from HAE with normal C 1 inhibitor indeed represent a tragic, unmet medical need until researcher's figure out the exact pathophysiological mechanism that triggers swelling in these patients. A recent paper in the proceedings of asthma and allergy entitled hereditary angioedema with normal C 1 inhibitor function consensus of an international expert panel, provides specific criteria for the diagnosis of HAE with normal C 1 inhibitor. It is important to note that the paper cites reports in which medicines licensed to treat patients who have HAE C 1 inhibitor deficiency have been helpful when given to those suffering from HAE with normal C 1

inhibitor levels. The paper properly recommends clinical studies to ascertain which drugs are truly effective for the treatment of HAE with normal C 1 inhibitor. Until the studies are completed however, the morbidity and potential mortality associated with this diseases could be alleviated by a regulatory pathway that would expand the labels of currently approved HAE therapies to include treating the subpopulation of HAE patients with normal C 1 inhibitor.

The benefit risk profile of providing these patients with what I call an expanded label alternative regulatory pathway, is unequivocally favorable given 1, the unmet medical need hardship faced by this patient subpopulation; 2, evidence indicating that medicines licensed to treat HAE C 1 inhibitor deficiency can help these patients; and 3, the apparent excellent safety profile of the licensed therapies. Most importantly, any potential inappropriate use of these medicines would be mitigated by the recent publication of definitive diagnostic criteria for HAE with normal C inhibitor. In addition, the expanded product labels could advise judicious and in ascertaining clinical efficacy to justify the continuing of therapy.

In summary, HAE patients with normal C 1 inhibitor fit the criteria of limited criteria of unlimited criteria, well defined a subpopulation with a serious unmet medical need and provide a compelling, concrete and contemporary example of how an alternative of a regulatory pathway could be rudely applied. Thank you.

RACHEL SHERMAN: You get the prize for persisting comments today. Questions?

ISSAM ZINEH: Just to clarify the basis for expanded labels would be what? Would be literature that shows...?

ANTHONY CASTALDO: Last count may be nine studies that have been done in various centers around the world that have indicated and there are some theories about the pathogenesis to be sure. Each one of these therapies fit what we perceive, which we think is the primary medication but it just hasn't been worked out yet, so that's really----understand again certainly anecdotal but you are dealing with an unmet medical need and hereditary angioedema with C 1 inhibitor deficiency was a catastrophic unmet medical need until the first approval of the Cinryze C 1 inhibitor product in 2008. We really understand what these patients are going through. It seems to me, since we have specific criteria now to diagnose who these patients are, and we have wonderful group of physicians with experience in dealing with HAE, we can circumscribe this

group and have a really intelligent way to try to treat these patients and prevent death and significant morbidity.

RICHARD KLEIN: Maybe I missed it but in the context of changing the label, would you still envision clinical trials ongoing?

ANTHONY CASTALDO: Absolutely, I think I tried to make that clear with testimony here. We are looking at sort of a stop gap measure. In fact, interestingly enough in the paper I cited, the proceedings paper, the Hereditary Angioedema Association actually sponsored that proceeding and brought together the foremost experts in angioedema from throughout the world to put together the consensus document to A, workout a good working diagnosis to make sure that the sort and get the right subset and identify the subpopulation as definitively as possible and then the paper also said that the research agenda which is now happening in many centers throughout the world.

So, what this basically doing, offering the patients a chance at some therapy which evidence strongly suggests them do work on some patients, in the meantime while work this thing out. Again, as someone who had a child who almost died from HAE, wherein there were therapies available in Europe, safely used by sophisticated Western European doctors for 30 years, having to wait those five years or so for the process to get approval here was one I would certainly not want to happen again when we have good evidence that suggests for some patients these products could work.

RICHARD KLEIN: So will the data be collected in the context of the labeled use?

ANTHONY CASTALDO: As I would understand the process, if I was asked to comment upon how I would think this would work, I think you would have perhaps the industry could go for expanded label based on the studies out there, with a mention and caution for judicious use to ascertain efficacy, needs to be part of the process. Again, we have a very code rated allergy immunology specialists who really understands and works with HAE patients. That can be accomplished. Simultaneously, however there do need to be specific clinical trials that do leverage off what we think are the pathophysiological mechanisms, perhaps generating system for these patients and take a look, and simultaneously do randomized clinical trials, but in the meantime try to provide for those patients who may not be in a clinical trial, some sort of relief on some basis until we actually get these things worked out.

RACHEL SHERMAN: Other questions? Thank you for your comments. Our next speaker is Jennifer Yttri, National Research Center for Women and Families.

JENNIFER YTRRI: Thank you my name is Dr. Jennifer Yttri. I speak today on behalf of the National Research Center for Women and Families. Our non-profit research center includes scientists, medical and public health experts who analyze and review research to provide objective, understandable, health information to patients, healthcare providers and policy makers. My PHD is in immunology from Washington University. My statement today also reflects written comments of 14 members of the patient consumer and public health coalition. The coalition is comprised of nonprofit organizations united to ensure that medical treatments are safe and effective and to enhance the scientific and the public health focus of the FDA. I thank you for the chance to speak today.

Like everyone here, we recognize we need new drugs to be patients with serious or life-threatening disease we have grave concerns about how this is being predefined pathway will improve development of safe and effective drugs. The FDA already has six pathways to quickly get drugs to patients with unmet needs. So where is the evidence that this new pathway is needed? How will it promote development of drugs that help patients live longer or have a better quality of life? Almost 50% of the drugs approved in 2009 and 2011 were through one of these priority pathways. So there are many ways to get these drugs to patients.

In the PCAST recommendations from which the FDA's proposal was derived, the council said that touch a pathway would be ineffective without changes in FDA approval and regulatory processes to protect patients. PCAST said that the FDA would need to establish clear guidelines for clinical trials of drugs to prove benefit giving serious and unknown risks.

To emphasize the harm this pathway would cause to all patients without a change in FDA's authority regulate distribution after drug approval for one indication, without first addressing these major changes designing this new approval pathway is pretty premature. The FDA currently requires adequate and well controlled trials for drug approval. As you know there are inherent dangers when drugs are approved based on smaller and shorter clinical trials. The quality of the research is even more important when studies are done on narrow population. Small, short-term studies provided limited information about drug toxicity and safety. Small studies can also overestimate the benefit to patients. Surrogate endpoints have become common

in clinical trials, they still need to be appropriate and here's a list of examples when they are not appropriate.

A surrogate endpoint is valid only if it correlates with outcomes patients care about which is either health, quality of life or how long they live. The therapeutic must affect the surrogate endpoint in the same way that it affects mortality and morbidity. Quinomycin was great at killing mycobacteria with a higher mortality in patients with AIDS. It helped some patients with lupus get rid of the rash but that exchange leaves them susceptible to severe infection and death. Avastin slowed breast cancer progression but did not extend or improve patient quality of life, in fact it did the opposite. These are all cases where surrogate endpoints showed promise but in later studies proved the opposite. The proposed pathway can't promise improved health or quality of life or life span. It can try to make a drug available sooner, but shorter trials will have less information about whether the drug accomplishes any of these three patient centered outcomes.

Waiting for data from post market cities to identify safety risk means patients, will meanwhile pay for unproven treatments while patients will die or be harmed for years before post-market studies are completed. There is also the added complication for approving drugs on very small groups of patients. For many of these serious and life threatening conditions, specific target populations cannot be readily identified prior to clinical trials. A limited population pathway provides an incentive to create smaller trials but not ones that use appropriate studies with the right patients. This brings up the problem of off label use.

If these drugs are to be used in a limited population physicians need to prescribe these drugs only in patients who clearly fit the limited population and have no better options. This is unlikely to happen. Currently, 21% of all prescriptions and 62% of pediatric prescriptions are for unapproved use. Once a product is approved, it is likely to be taken by many patients who are not in the targeted population. In the case of antibiotics, a class of drug that is likely to seek approval through this pathway, in appropriate use, even just one does, will add to the problem of antibiotic wellness—resistance, the very condition we are trying to fight.

Since 2004, there have been 28 settlement companies and I list them here, that promoted drugs for unapproved use often targeting patient populations in these drugs have never been tested. Last year, major lawsuits were settled against GlaxoSmithKline, Johnson & Johnson and Amgen. This could change but not for the better. The FDA has so far done nothing to overturn the recent

case of United States versus Corion which decided that the pharmaceutical representatives can promote off label use under the First Amendment. The FDA has not developed effective strategies to stop off label promotion and therefore will not be able to restrict the use of drugs to the approved, limited population.

Additionally, a study by Chen et al found that physicians were barely above chance in knowing their prescriptions was off label or foreign FDA approved use, even though many of these doctors have prescribed the very same drugs for years. With widespread promotion, off label use, thousands of patients will be exposed to unnecessary harm before we understand what conditions these drugs work in and what the safety risks are. Worse yet, in another study, only 15% of medical providers stated that they provide safety information to patients if it is indicated on a drug label. A formal designation or logo will not help much. Even with some extended educational plan for clinicians or patients or medical guidance, most patients will not fully understand what extent the drug is proven safe or effective for their needs.

In conclusion, this pathway would promote unproven drugs to high-risk patients. We know they are desperate patients who are willing to take the risks, but with smaller, shorter trials you won't be able to tell either patients or the doctors what these risks are. If approved based on such limited information, there is no doubt that some of these drugs would harm more patients than may help. Patients, some of whom would never benefit from these drugs, will die or be irreparably harmed.

So there are already six expedited pathways used to approve almost half of the new drugs. I share the FDA's desire to help patients with unmet needs get access to drugs that could possibly help them. I wish there were a way to do so without jeopardizing patients who have other treatment alternatives, or who are unlikely to benefit, wishing isn't science. The FDA is a scientific agency and it has not provided the science to support this proposal. Thank you.

RACHEL SHERMAN: Thank you for your comments. Questions?

ISSAM ZINEH: Just a question about your last statement regarding alternative therapies. So what if there weren't alternative therapies? In other words, you identified a subset of patients where no treatment is available, can I infer from your talk that you think one of these other pathways would be appropriate mechanism to develop drugs for that subset? Or can you maybe clarify your comment about lack of available therapies?

JENNIFER YTRRI: Correct. We believe that the six pathways the FDA already has implemented, some of which are rather new and according to advisory committees, they don't actually understand how to implement these pathways to begin with. We feel that there are already strategies to get some of these drugs out to patients and we don't understand how this new proposal will actually fit in with those systems or if those other pathways are over utilized as is. That is kind of information we would like to see the FDA produce before they get into something like a new pathway.

RACHEL SHERMAN: Other questions? Thank you for your comments.

JENNIFER YTRRI: Thank you.

RACHEL SHERMAN: our last scheduled speaker is Mark Velleca from the Leukemia and Lymphoma Society.

MARK VELLECA: Thank you. My name is Mark Velleca. I am the chief policy and advocacy officer for the Leukemia and Lymphoma society. I am also a physician and scientist. Prior to joining LLS I spent in academic medicine and 12 years in the biopharmaceutical industry leading teams that brought multiple, small molecule drugs from bench to bedside to patients with autoimmune disease and cancer.

LLS is a six year old 501 C3 patient organization that represents the 1 million plus patients afflicted with bio cancers such as leukemia, lymphoma, Hodgkin's disease and multiple myeloma. We appreciate the opportunity to participate in this important public hearing and provide comments on questions posed by the FDA regarding this proposed alternative approval pathway. I will specifically address questions one, two, three and six from the register.

Question one, will this type of pathway increase their pick options for serious conditions where an unmet medical need exists? Yes, LLS applauds the FDA's initiative to create a potential new pathway to expedite the development of new drugs for serious or life threatening conditions would address unmet medical needs. The concept of a limited use pathway could accelerate the development of new therapies and present opportunities for blood cancer patients to have more timely access to precision medicines.

Question two of the FDA has requested that we identify specific as serious or life threatening conditions for which an unmet medical need exists and for which the approval pathway may benefit subpopulations of patients. LLS believe that it has the expertise to help the FDA to identify these conditions. Since our founding in 1949, we have invested almost \$1 billion on research for cures of life threatening hematological malignancies. The research has touched or directly supported all the therapies that have been approved by FDA for blood cancer in the last 40 years. Because the ready accessibility of blood cells are understanding the molecular diverse of blood cancer is at the cutting edge. Building upon breakthroughs in genomics, epigenomics, and proteomics, we have identified critical pathways amenable to therapeutic intervention.

Despite these insights, there are many obstacles that still remain such as the high cost and extended timelines of developing drugs for small patient populations. The novel precision medicines being developed to treat the hematological malignancies, will inherently benefit small populations of patients. I will give work active examples of unmet medical needs of the novel therapies being funded by LLS that are currently in development that may be accelerated by special approval pathway. First is the pioneering immunotherapy research being done at the University of Pennsylvania led by Carl June using genetically engineered autologous T Cells for patients with leukemia who have relapsed after standard treatment. The New York Times recently featured a front page article about Dr. June's breakthrough immunotherapy.

Of twelve cancer patients treated to date, four have experienced sustained, complete remissions. The article chronicled the experience of one of those patients, Emma Whitehead, a six year old who was near death from relapsed acute lymphoblastic leukemia. Emma is now cancer free and in remission for six months.

Second, at the University of California San Francisco, there have been recent advances in understanding the genetic mutations that cause an especially lethal form of leukemia in children, called juvenile myelomonocytic leukemia. The researchers' findings have led to a new molecular test used to diagnose this type of leukemia and has uncovered novel therapies addressing these pathways.

Testing of two drugs is already underway; one of which was first developed for adults with a different type of myeloid malignancy.

Third, Dr. John Byrd is leading a research team at The Ohio State University where they have reported positive clinical trial results for patients with relapsed / refractory CLL. Patients treated with ibrutinib in combination with the monoclonal antibody drug Rituximab. Ibrutinib could be approved under an alternative pathway for advanced stage CLL patients while clinical trials continue for treatment-naïve CLL patients.

Fourth, researchers at MD Anderson Cancer Center are developing anti-cancer vaccines for patients with follicular lymphoma. This program includes individualized anti-tumor vaccines, based on the unique proteins produced by each patient's particular lymphoma. In all four of these examples, it is clear that large, randomized trials are simply not feasible; therefore an expedited pathway for approval could greatly accelerate the availability of these treatments to all patients who meet the diagnostic criteria of the particular subpopulation.

It will be critical for FDA to define terms such as "limited-use," "serious conditions," and "well-defined subpopulations" in order to understand how inclusive this pathway will be. As stated above, every blood cancer is a serious or life-threatening condition; several of the therapies in development will be used in small, well-defined patient populations, many of whom share a risk tolerance that is much higher than in the overall population.

Question 3: What approaches could be undertaken to monitor use of drugs approved under this pathway to determine whether they are being used consistent with the terms of approval?

While LLS understands the desire to manage or limit use in a broader population where safety and efficacy have not yet been demonstrated, we are concerned that efforts to discourage off-label use could impair legitimate access to drugs that are approved for limited uses. The Federal Register notice specifically mentions antibacterial drugs where there is a public health interest that extends beyond the protection of each individual patient. However, in the treatment of blood cancers, no such "additional" public health interest exists. Oncologists make difficult decisions with their patients every day about how to balance the risk of life threatening side effects against the possible benefits. The FDA should not have a single approach to these differing situations.

LLS believes that efforts to ban evidence-based off-label use for drugs approved through a limited-use pathway or to impose penalties for using a drug outside the approved population imposes undue rigidity to an oncologists decision making process. There are numerous examples

of oncology drugs that were used "off-label" but, guided by solid medical and scientific evidence, those drugs demonstrated efficacy in additional indications. Perhaps the best known case is the use of Imatinib in patients with gastrointestinal stromal tumor (GIST). It is appropriate to preserve a physician's ability to prescribe drugs off-label under these types of situations.

Question 6: We were also asked whether the use of a formal designation and logo to reflect approval under this pathway, with clear labeling of clinical information supporting use only in the indicated subpopulation, but without other constraints from FDA, would be effective in limiting use to the indicated subpopulations. We believe that a formal designation to reflect approval under this pathway should suffice to limit use to the indicated subpopulation. The use of a companion diagnostic could also be a powerful tool to guide usage to the appropriate patients.

In summary, LLS recognizes the importance of alternative and expedited approval pathways and the impact these pathways have on the blood cancer community. Imatinib was granted accelerated approval for the treatment of CML in 2001 and has now saved thousands of lives. Collectively, we need to ensure that there is an appropriate pathway for the many new immunotherapies, precision medicines, and other potential lifesaving advances currently in development. Hundreds of thousands of blood cancer patients are waiting for these therapies so that they can lead longer, better, healthier lives. LLS look forward to working with FDA on this important initiative and to providing FDA with informative and reliable research and clinical data.

Thank you very much for convening this meeting and for seeking public comment.

RACHEL SHERMAN: Thank you for your comments. Questions?

Thank you. We have now reached open public comment, and no one has registered.

Is there anyone present who would like to speak? Is there anyone who has spoken and has more to say? Is there anyone on the panel who would like to question a previous speaker if they are still here? Ok, you guys are very efficient.

On behalf of the FDA I would like to thank the speakers for their presentation and all the audience whether in person or by webcast, for your attention to the issues discussed in today's

meeting. I would also like to call your attention to the Federal Register Notice, the docket which will remain open until March 1st. Again I encourage you to please submit not only your presentations but any additional information you might have that will help inform the agency as we consider this. We take the docket very seriously and would really appreciate your comments.

I would also like to thank the office of medical policy staff who once again put together a flawless meeting; Jonas Santiago, Melissa Raab, Jim Ward, Kayla Garmon, Marcia Hollman. Lauren Myers, Nicole Silva, Annie Benton and Connie Wisner. We had a very full day. It was very interesting, actually not that full, we are well ahead of schedule. It was very interesting, very insightful, very thought provoking. We will consider all the comments and as I mentioned on the comments in the docket, in our decision making and as I alluded to, is not the beginning and the end. This is part of a continuing process as we consider these issues.

Today's meeting is concluded. Thank you for your participation and have a safe trip home if you are travelling.

[Whereupon at 3.17pm the meeting was concluded]