

Food and Drug Administration Public Hearing:

Considerations Regarding Food and Drug Administration Review and Regulation of
Articles for the Treatment of Rare Diseases; Public Hearing

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Day 1 Meeting Open

Timothy Coté:

Okay, welcome everybody, and thanks for coming. Good morning and welcome to FDA's open public meeting on the topic of the review of articles that is drugs, and biologics, and medical devices used in the treatment of rare diseases. My name is Timothy Coté, and I serve as the director of FDA's Office of Orphan Products Development, which is in the office of the commissioner. Additionally, I serve as the chairman of the Expert Committee, mandated by Section 740, which was an amendment to FDA's appropriations bill. The law mandates that FDA convene a committee of expert FDA employees to consider the ways that the agency reviews articles to treat people with rare diseases, and consider policy improvements that might help people with rare diseases get better treatments faster.

While the law says virtually nothing about the expert committee receiving public input, we're gathered here today because such policies would affect everybody, the patients and their families, the advocacy groups that represent them, the biotech industry, and academics they partner with. So, it's only natural that we set aside time to hear the reflections of those engaged in the endeavor of making miracles and those who desperately need them, to hear your concerns as the process stands now and your visions on how it could be or how it should be. Today I'm joined by Dr. Elizabeth McNeil to my left, who serves as the executive secretary for the Section 740 Committee. It is she that will actually draft the commissioner's report to Congress and guidance documents that flow from its contents. I'm also joined by representatives from each agency's major review division centers, the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and the Center Devices and Radiologic Health. The representatives of these centers may change over the course of the two days of the meetings, but the chairs will remain occupied by active listeners.

This meeting is being conducted under the rules of Part 15, which is an official mechanism for soliciting public input. Beyond these introductory comments, I and my colleagues from FDA will contribute very little to content of the next few days. Though we may offer the occasional question of clarification, it's basically your meeting. We're not here to answer questions but to hear from you how you believe, as an agency, we should proceed towards a review process that yields more and better new drugs for people with rare diseases. On the agenda, it seems we have quite a lot to listen to. There's a wide variety of speakers, ranging from patients and advocates to industry and other interested parties, many of whom are very long established members of the rare-disease community and a few who are less mainstream. This is good. I expect that the committee will hear both conventional and innovative ideas on the topic. Before we get started, please permit me to make a few comments on where we've come from on our current state of affairs in making drugs for people with rare diseases. Then it will be you who will answer the question of where we're going.

In 1982, the world was a much different place for people with rare diseases. Over the preceding 10 years, fewer than a dozen drugs had been developed for people with rare diseases. The basic model for the pharmaceutical industry was that you create a new drug, and then you sell it to patients to recoup your development costs, and you battle it

out with whoever else was trying to get on the new market that you created. This market scenario was very unattractive, and hence, hardly any companies undertook the development risks. The Orphan Drug Act of 1983 changed all that, most importantly by establishing a seven year marketing-exclusivity period that made the business model work. Over the subsequent 27 years, FDA has designated more than 2,200 products with promise as orphan drugs. And from those, our review divisions have approved 358 for marketing, because they were found to be safe and effective.

The credit for these successes must be given where it is due. First and foremost, it was driven by parents and those who struggle on their behalf, by patients and those who struggle on their behalf. There are none among us so unstoppably motivated as a parent who's seeking a cure for their sick child. And secondly a whole biotechnology sector grew up around the past 27 years with the implantation of the Orphan Drug Act. The drugs have not come from government programs, but from independent genius, innovation, and willingness to take risk. And lastly, the FDA review divisions have been populated by people of extraordinary sensitivity and sensibility, who have flexibly applied the same regulations that govern all FDA approved drugs. That is, the requirement that they be clearly shown to be safe and effective to these orphans, approving drugs sometimes on the basis of experience with extremely small numbers of study subjects, but still demanding incredible evidence of safety and effectiveness.

Abbey Meyers, that housewife from Connecticut and grassroots organizer from Danbury, Connecticut who went on to pass the Orphan Drug Act and led a movement called NORD, I always held that it was a matter of Civil Rights that rare-disease patients are entitled to drugs that are safe and effective just like common-disease patients. It was for this reason that the Orphan Drug Act's [unintelligible] to [unintelligible] drugs was based on the change in market-place math, not a change in standards of FDA approval.

And now we arrive at the crux of today's meeting. For those 7,000 rare diseases, and the vast majority of them still have no therapies at all, the FDA policy regarding the review of drugs and biologics for rare diseases is no policy at all. They are held to the same standards of safety and efficacy mandated for all pharmaceuticals. And though we've accumulated a large collection of new therapies for rare diseases and the basis of their approvals has exemplified flexibility and reasonableness in FDA's evidentiary demands, this is done on a case by case basis. The process has been practical and very productive, but the policy remains, no policy.

So, the questions that we put to you, the public, albeit more eloquently written in the federal registry notice, which we on the committee are asking ourselves, and which you will answer today is, is it working? Do we need a policy? If so, then what? In one of first publications, after becoming FDA commissioner, Dr. Margaret Hamburg related that the agency has often been confused of approving drugs at only two speeds, too fast or too slow. How do we find the right balance for drugs for people with rare diseases? Today, FDA's marketing approval means that we know that a drug really works, not that we think that it might work, and that it's reasonably safe. How do we defend that standard while reckoning with the great urgency of now experienced by the parent of a sick child? Answers to these questions are found not only in regulatory science, but in the will of the

people. Gratefully, you have answered our call to democratic participation in this process as we prepare our report for the commissioner to Congress. We cannot do it without you.

We best get down to our long day of listening. And I think we're ready for the first speaker. Paras, I think that you had a couple of introductory logistical comments, and then we'll take our first speaker.

Paras Patel:

Good morning. Welcome to the White Oak facility. I'm the project manager, my name is Paras Patel, for this public meeting, scheduled for June 29 and 30. The meeting today is being transcribed and will be submitted to the public docket, docket number FDA-2010-N-0218. The transcription will be sent to www.regulations.gov, and will be open for public comment until August 31, 2010. When you come up to the podium, I'll be introducing the speaker. There is a clicker that's been provided. Please state your name and organization, and we'll go ahead and get started. So, our first speaker today will be Dr. Saltonstall and Frank Sasinowski.

First Session

National Organization for Rare Disorders

Frank Sasinowski:

Thank you Paras Patel and thank you Dr. Cote, Dr. McNeil. Good morning, the National Organization for Rare Disorders or NORD welcomes this opportunity to be the initial presenter at the FDA's first public hearing on rare disorder therapies. I'm Frank Sasinowski, chair of the board of NORD, and we want to share our views on the FDA's exercise of its responsibilities for regulating therapies for Americans with rare disorders. NORD is a leading advocate for the 30 million Americans with rare disorders. NORD is justifiably proud of our history as a principal force behind the effort that culminated in the 1983 Orphan Drug Act. And NORD is just as equally proud of our current activities to advance the interests of Americans who have one in 6,000 rare disorders.

I only have time to list some of NORD's major initiatives over the past 13 months. First, NORD organized a full-day summit on orphan disorders at the Ward Hotel in May 2009, chaired by former FDA Commissioner Kessler and key participants included Dr. Janet Woodcock and Dr. Francis Collins. A summary of this summit is available on the NORD website. Two, NORD, with the assistance of John Crowley CEO of Amicus, one of NORD's corporate council members, was responsible for organizing a Congressional caucus on rare and neglected diseases this year. Three, NORD was a key player involved in Section 740 of the fiscal year 2010 Appropriations Act, the so called Brownback-Brown Amendment, which is the impetus for this hearing here today. Fourth, NORD suggested and supported that the FDA and the Center for Drug Evaluation and Research, CDER, establish its first position dedicated to issues related to the regulation of medicines for those with rare disorders. And in February, the FDA created a post of CDER associate director for rare diseases, and I see Dr. Pariser here today. Thank you, Dr. Pariser, for all your efforts on behalf of those with rare disorders. Fifth, NORD worked for the passage of comprehensive healthcare reform. And in particular, those two provisions of vital interest to those with rare disorders: one, eliminating preexisting

conditions and two, eliminating lifetime and annual insurance caps. To see that what was gained in Congress is not lost in the courts, NORD is currently participating in an Amicus brief to defend the constitutionality of the healthcare reform law. Sixth, NORD, with the involvement of FDA Commissioner Hamburg and NIH Director Collins, set up a task force on rare disorders in January. In several meetings at which senior FDA and NIH officials participated, and I see some of them here today like Dr. Walton, NORD has explored ways to facilitate the development of therapies for rare disorders, including holding a series of four focus groups, each separately meeting with representatives of patient organizations, the medical and scientific research community, the pharmaceutical industry, and the financial-investment community. And seventh and finally, on the 7th day, NORD rested.

Both at the NORD summit last May and at the NORD task force meetings, including the focus groups, NORD has learned much. We want to share some of those key findings with the FDA today. First, over the 27 years since its enactment, the Orphan Drug Act has proven a resounding success. This is best seen in the over 350 new medicines for more than 200 different rare disorders approved by FDA over the first quarter of a century of the law's existence. However, what NORD learned at its summit and in its taskforce proceedings that there are still about 5,800 disorders for which there are no FDA approved therapies. Perhaps most discouraging is that many affected with these rare disorders do not even see any research being conducted in their conditions. For NORD, this seems as though the proverbially low hanging fruit have already been harvested in the first quarter of a century of the law's existence, while the vast majority of therapies are currently out of reach of those in need of an FDA approved medicine. In sum, much has been accomplished by FDA, by NIH, by medical and scientific researchers, by the pharmaceutical industry, by the financial community, and by patient advocates in these first 27 years, but much, much, much, much more beckons each of us to respond to the needs of those with rare disorders.

So, second, how best can each of us respond to those in need of therapies? As part of the NORD task force, NORD, with senior FDA and NIH officials in April, held a series of four focus groups to listen and learn. What are the barriers slowing or barring the development of new therapies for rare diseases, especially the 5,800 rare disorders for which there are no FDA approved medicines. We had a separate focus group with each of the four major stakeholders involved in developing new therapies, the patient community, the academic-research community, the pharmaceutical industry, and the financial-investment community. In those separate task force proceedings and at the NORD summit, we heard many ideas. Several of those ideas would require new legislation, and so those are beyond the scope of today's hearing. What we at NORD heard, which can be addressed by FDA, is the benefit that would be gained from FDA action on the following two recommendations. First, for a clear, more granular expression of FDA's historic commitment to exercise flexibility in its review of therapies for rare disorders; and two, for an FDA expression of ways to reduce regulatory uncertainty in the development and review of orphan-drug therapies. Let's explore each of those.

NORD's first recommendation is for an FDA statement of policy on FDA's historic flexibility on regulating orphan drugs. NORD heard, especially from the investment

community and the pharmaceutical industry, that FDA delivers a consistent, repeated message that the statutory standards for safety and efficacy are the same for both rare disorders and prevalent diseases. What is not often heard is the companion portion that completes that statement, which is that while the statutory standards are the same, the FDA interpretation and application of those same standards have historically been tailored by FDA to the unique facts of each particular medicine for each particular rare disorder under FDA review. Moreover, there are FDA regulations and guidances that express this flexibility. In addition, FDA actions are marking applications eloquently embrace and express this concept of flexibility. This exercise of FDA scientific judgment in applying these statutory standards flexibly to various situations, apparently, is not being heard by some of the key stakeholders in this system.

So, today NORD is asking the FDA to develop an issue, a specific statement of policy on FDA's role on regulating therapies for rare disorders, which includes an explanation and affirmation of the FDA's historic position that FDA flexibly applies the standards of safety and effectiveness with respect therapies for those with rare disorders. What we at NORD have heard is that the investment community and pharmaceutical industry may benefit from such a formal, explicit statement of policy that will encourage investment in, research of, and development of medicine for those with rare disorders, especially for those 20 million Americans with one of the 5,800 rare disorders for which there is still not a single FDA approved therapy.

So, let's look at some of those elements that I mentioned. First, FDA regulations and guidances that speak to this flexibility. In responding to the AIDS crisis that was becoming apparent around the same time that FDA was implementing the Orphan Drug Act in the mid 1980s, FDA promulgated subpart E of the I and E regulations for "Drugs intended to treat life threatening and severely debilitating illnesses." FDA stated that the purpose of subpart E is "to establish procedures designed to expedite the development, evaluation, marketing of new therapies intended to seek persons with life threatening and severely debilitating illnesses, especially where no satisfactory alternative therapy exists." As stated in section 314.105(c), "While the statutory standards of safety and efficacy apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for those drugs demand flexibility in applying the standards. The FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards while preserving appropriate guarantees for safety and effectiveness." I mean, I am still quoting from the FDA regulations. "These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life threatening and severely debilitating illnesses than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated."

This regulation that was referenced, the regulation that was referenced in the subpart E regulation is section 314.105(c), which even predates the subpart E regulation, and illustrates, again, FDA's historic position on applying the same statutory standards in a flexible way depending upon the circumstances. Section 315.105C states, and again indulge me for quoting extensively from the FDA regulations, but I wanted you to see that this is the FDA's regulation speaking and not just NORD interpreting or applying.

This is the FDA regulation. So, section 314.105(c) states, “The FDA will approve an application after it determines if the drug meets statutory standards for safety and effectiveness, manufacturing controls, and labeling. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for these drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data information an applicant is required to provide for a particular drug to meet these statutory standards. FDA makes its views on drug products and classes of drugs available through guidelines, recommendations, and statements of policy.” So, that’s why we are NORD are asking for an explicit statement of policy on FDA regulation of therapies for orphan disorders.

An example of the formal regulatory policy or guidance that expresses this concept of flexibility in FDA’s application of statutory standards of safety efficacy is seen in the ICH E1A guidance. That FDA adopted international guidance stipulates the minimum quantum of safety exposures necessary for FDA to even accept a marketing application for review when the medicine is intended for a chronic condition. Most rare disorders are chronic in nature and not acute. And so this guidance applies to most rare disorder therapies. That guidance states that the minimum number of safety exposures to meet the statutory standards for safety are 1,500 persons exposed to an investigational therapy, with 300 to 600 of those exposed for at least six months, and at least 100 exposed for a year. However, the guidance also states that these minimum safety thresholds do not apply to therapies for rare disorders. Importantly the guidance then does not state what is required in the alternative, whereas it could have stated an algorithm, such as at least one percent of the U.S. population with the rare disease must be exposed with half of them for at least a year. No, instead the guidance relies upon the exercise of FDA scientific judgment to determine what is appropriate to meet the statutory standard for safety in each particular rare disorder therapy.

So let’s also then look at particular marketing applications because those are illustrative. Instead of reviewing many such precedents, NORD refers to but one recent example as an illustration. In March of this year, FDA approved Carbaglu for NAGS deficiency, the rarest urea cycle disorder, with only 10 patients in the U.S. generally at any one time. In the FDA briefing document for the January 13, 2010 advisory committee, FDA explained that while Congress in 1962 added a new statutory standard requiring that a drug prove its effectiveness, “Then according to the FDA, FDA has been flexible within the limits enclosed by the Congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on the particular drug are convincing. Thus the evidence obtained from retrospectively-reviewed-case series could be considered as substantial evidence of effectiveness. The fact that the case series, here, presented in this application is retrospective, un-blinded, and uncontrolled precludes any meaningful formal statistical analysis of these data. Under these conditions any statistical inference from confidence intervals and or p-values is uninterrupted, and consequently should not be utilized to inform decision making.” It also illustrates the flexibility. That is why we took a recent example.

I just went to last week and looked at Dr. Jesse Goodman’s statement last week to Congress. Dr. Jesse Goodman, the FDA chief scientist and deputy commissioner for Science and Public Health, testified last week before the Senate Appropriations

Committee, Agriculture Subcommittee on, "FDA's efforts on rare and neglected diseases." In Dr. Goodman's commendable testimony, he cites to the Carbaglu example as well as several others to illustrate that "FDA is fully committed to applying the requisite flexibility in the development or review of products for rare diseases while fulfilling its important responsibility to assure the products are safe and effective for these highly vulnerable populations. There are numerous examples of drugs approved for treating rare diseases where FDA's flexibility and sensitivity to the obstacles of drug development for rare diseases have brought forth a successful treatment."

And then I would like to conclude this series as I walk through the regulations, guidances, FDA statements with a personal example. In a meeting I had this month with the FDA, the FDA told a sponsor at an end of phase two meeting for a therapy to treat a very troublesome symptom of a very serious but common, that is prevalent, not orphan, disease but the sponsor had not only to prove the effectiveness of the drug to treat the symptom, but also the sponsor had to rule out that the drug did not increase unacceptably the risk of death in that patient population with a serious disease. FDA stated that the sponsor would have to show what increase in the risk of death could be excluded by reference to the upper 95 percent confidence interval. While we did not at that meeting arrive at an agreement on the size of the magnitude of the risk that had to be excluded, even ruling out only the doubling of the risk of death would likely require a study of thousands of subjects for a long period of time. While I had been involved scores, maybe hundreds, of therapies for rare diseases, I have never heard FDA express a similar requirement for the therapy for a rare disease. Why? This is likely because FDA is being flexible in interpreting and applying statutory standards for safety and efficacy, and that FDA knows that to require a similar type of showing for therapy for rare disease would be impossible. For almost all orphan drugs, there is a limited pool of potential subjects for clinical trials. The statutory standards are the same both for the prevalent disease and the orphan condition, but FDA rightly interprets and applies the standards in light of the disease and the investigational therapy.

In other areas, too, FDA can exercise similar flexibility, for instance, when the potential number of subjects is limited the degree to which FDA demands dose selection be optimized and preapproval studies may be reduced. As can be FDA's requirements for validation of patient-report-outcome instrument in a rare disease population, though proof of the sensitivity, specificity, and clinical meaningfulness of a primary end point, given that each investigational therapy for a rare disorder will present unique features. NORD understands that the granularity of the requested statement of policy on rare disorder therapies may necessarily be limited. However, even cataloguing the nature and scope of the orphan drug precedents that illustrate FDA's flexibility may enable key stakeholders to better understand FDA's position. That is, even while FDA states correctly that the statutory standards are the same for prevalent and rare diseases, FDA will have a formal companion statement of the equally important and consistent FDA's historic position that FDA will exercise its scientific judgment to interpret and apply those statutory standards in a flexible manner tailored to each rare disorder therapy.

NORD looks forward to the FDA issuance of an FDA statement of policy on FDA's regulation of therapies for rare disorders, and to the day, when every FDA official who speaks to patients or other stake holders, including researchers and sponsors, about the

FDA's policies on regulating therapies for rare disorders, does so in a complete and balanced way that Dr. Goodman did just last week, when he testified. Both that as to the identical statutory standards that rare disease therapies must meet, as well as to the historic FDA flexibility in interpreting and applying those standards, exercising FDA scientific judgment in light of the particular circumstances of that unique rare disorder and specific investigational therapy.

Second NORD recommendation is to reduce regulatory uncertainty in the development of medicines for rare disorders. In addition to the willingness of persons with rare, serious diseases to accept more safety risks and less rigorous evidence of effectiveness than for a prevalent disease, or for a less serious disease, or for one with some already approved therapy. And in addition to the learning that some key stakeholders would benefit from a formal FDA statement of policy on FDA's exercise of flexibility, the other consistent message that we at NORD learned, from our research and interactions since the NORD summit in May 2009, was that the development of therapies for rare disorders could additionally benefit from a reduction in regulatory uncertainty.

It is axiomatic that the perfect is the enemy of the good. In the world of rare disorders, there is much that is often not known or not known well, starting with the ideology and the pathophysiology of a condition including its natural history and ranging to a lack of agreement among even a small handful of world experts on the most common clinical manifestations of some conditions. Against this backdrop, it is entirely understandable that FDA on occasion will find it difficult to concur in advance with a development program, even the design of a registrational trial under a special protocol assessment. However, researchers, industry, and FDA, as well as, most importantly, persons with the condition may find that sometimes a study needs to proceed because patients are suffering and cannot wait until the perfect trial design with the ideal primary end point to be eventually determined or developed and consensually acceptable.

Research resources in the universe of rare disorders are precious. With the most precious being the persons with the rare disorders who are heroically volunteering to participate in a trial, usually under conditions where there is less known than in trials of therapies for prevalent diseases about the safety and potential effectiveness of the investigational therapy from animal models, animal toxicology, early human trials. So, when these trials aren't conducted, sometimes with designs with which all parties may not be in full concurrence, including the FDA, great deference should be afforded the design of these trials, and flexibility applied in the interpretation of these results. That such a principal would be addressed and accepted by the FDA, much good would come of it.

So, in closing, on behalf of all those with rare disorders, NORD commends the FDA on its stellar, worldwide-leadership role on orphan drug issues for the past 27 years. And NORD exhorts the FDA to continue to embrace even more fully the historic flexibility FDA has long noted, an exercise in FDA's regulation of medicines for those Americans with rare disorders and to [unintelligible] with ways that can be managed by FDA to reduce the regulatory uncertainty in the development and review process. NORD, for its part, commits to do all it can to continue to provide input to FDA on matters related to FDA's vital responsibility to the liberation of investigational therapies for each of the 30 million Americans with rare disorders and especially for those more than 20 million

Americans who have the 5,800 rare disorders for which there are no currently no FDA approved therapies. Finally, FDA would like to publically and formally express NORD's deep appreciations of the FDA for holding this hearing today on these critically important issues to so many Americans. Thank you Doctors Cote, McNeil, and your fellow FDA colleagues. I want to note that the statement that I've just given is going to be on the NORD website. Mary Dunkworth [spelled phonetically] promises that it's going to be up as soon as I finish. So, it should be on, Mary if you are hearing me, now. And I want to give a shout out to all those NORD officials who are watching on the webcast in the NORD offices in Washington, D.C. and in Danbury, Connecticut, keep up the good work. And I am going to put copies of NORD's statement n the back table in the back.

Timothy Coté:

Thank you Mr. Sasinowski, are there any other clarifying questions from the panel?

Paras Patel:

Next we have Seamus Thompson.

Second Session

Statistical Analysis Center and Mailman School of Public Health

Seamus Thompson:

Thank you very much. My name is Seamus Thompson. I am an applied statistician and director of the Statistical Analysis Center in the department of biostatistics at Columbia University. And this is [unintelligible] with my colleagues, Alexandra Sanford and Bruce Levin, who is the chair of the department of biostatistics at Columbia. I have been working for some years on NIH trials, primarily for the NINDS. And Dr. Stoveman [spelled phonetically] is the director and her colleagues Dr. Kaufman [spelled phonetically] and Dr. Korashatz [spelled phonetically] are deeply committed to a program to develop applications for rare diseases.

Regarding our initial response to question one for this hearing, and it's an honor and a privilege to be here today, as you know new therapies for rare diseases are fairly subject to the same review process and statutory standards regarding the demonstration of safety, and efficacy, and effectiveness in product quality as drugs for patients with non-orphan diseases or conditions, and everyone in this room is well aware of that. And in response to your question, I would have to say it's a very direct question, the practice does not meet the special needs of the very many patients who suffer from one of the rare diseases and who are running out of time and lack of therapies. And as the announcement for this hearing says, for most of the estimated 7,000 rare diseases that affect an estimated 30 million Americans, no approved therapies exist. And there's a corresponding number in Europe I believe of about 25 million patients.

Having begun to work in this field, our position at the Statistical Analysis Center, which is an applied unit, which develops innovative theoretical designs, statistical designs for clinical trials in general, but large clinical trials for rare diseases, and works with clinicians to implement those and also to incorporate advanced blood-based management systems to help in the efficient implementation of these trials. Our position

is that the review process for very rare diseases needs to be recalibrated in a way that remains compatible with the FDA's historic and admirable commitment to patient safety. Of course, the appropriate bounds of safety versus efficacy in the development of new, potentially life-saving therapies is completely central to the FDA's mission. However, this balance is currently balanced appropriately as it is generally applied in our perception for relatively common diseases and not for rare, severe diseases. So, we do think an adjustment of the calibration is required, and that despite current heroic efforts, we do feel that the Office of Rare Disease Research and the FDA, in general, are not appropriately equipped to succeed in their mission.

Now, as an example, we are working with Niemann-Pick Disease Type C, which is an autosomal-lysosomal-storage disorder. It's characterized, invasive rare disease, characterized by progressive nerve degeneration, early death. There are about 130 patients in the U.S. with this diagnosis. That's almost certainly an undercurrent. The natural history is not well understood. This is a typical situation with rare disease. We need disease-specific testing. We need and do not yet have appropriate end points. We need appropriate outcome measures. Currently no drugs are approved for treatment in the U.S., and two candidate therapies are available, but the small number of patients is of course a huge obstacle. This is a problem that we typically face. So, we've worked and put together a statement in general terms of the components that would be needed for an appropriate overall strategy for such diseases, taking Niemann-Pick Type C as a paradigm or typical exemplary case.

So, well, in terms of what we would like to have, we think that we want procedures that are comprehensive. We would like to recruit, if possible, all of the patients with a fairly confident diagnosis as rigorous as possible of Niemann-Pick C for trials and preliminary research. It's essential to optimize efficient collaboration among all the stakeholders to streamline the process as much as possible without, of course, sacrificing the principals of scientific rigor and patient safety. These are, however, easy things to say. I am well aware of it, but we will get to some suggestions shortly. And so we've been working with all the stakeholders involved in Niemann-Pick C to develop an advanced and useable database, which includes the data which is needed. That's what the investigators need, it's what the NIH needs, and which the FDA needs to identify and test an approved therapies. So, we need data on natural history. We need data on safety. We need data on outcome measures. And we need data on [unintelligible] medications. And since we are in the department of biostatistics, we are focused closely on developing clinical-trial designs and statistical procedures which are appropriate for very small numbers of patients.

So, on the statistical dimension, we are reviewing and tabulating the options which are available, and there are always tradeoffs, and each of these has a possible strength, and all of them as you very well know have weaknesses. So, we can have one study that applies to one patient, [unintelligible] generalization beyond one patient that can provide a controlled way of investigating, say, different doses. And being a double-blind way for one patient, there are designs for two to five patients. There are futility designs, crossover designs, assured allocations, SMART trial designs, and so on. I'll comment a little on the assured-allocation design as being particularly promising. Now, this design requires only a reliable prognosis for those who are not on the experimental therapy. And

unfortunately for very rare, severe diseases we can frequently deliver a very reliable and dire prognosis. If we have that accurate prognosis than all the patients can receive the experimental therapy and we can compare, in a very rigorous statistical way, their outcome to the projected outcome for those who are not on the experimental therapy.

And speaking as a member of the dedicated RCT thought police, someone who always runs a randomized design if it is at all possible, is deeply committed to randomization. I would say in this case, yes, this is not a randomized design, but it is unethical, in this case, to use a randomized design. It's not ethical to ask patients suffering from a fatal disease, where there is no known therapy, and it is known that conventional therapy will have no benefit, and the patient faces imminent demise, we cannot ethically randomize those patients to no therapy versus the experimental therapy. So, this is an efficient and powerful design which allows us to evaluate experimental therapies in the special case in a rigorous and satisfying way. So, it is not the only possibility but it is an attractive design, which can be used to good effect with a very small number of patients. And this is the sort of design that we should explore, and do the best we can with. It will answer and they will not answer all questions, but I think we can be perhaps better by exploring these than we have done. So, those are the references.

So, for the actual project, which is being proposed, and which is under read by agencies, and which I think could be generalized, here's the scope of a project for such a rare disease as Niemann-Pick. So, we are working closely with all stakeholders of the proposal that is to work closer with all stakeholders, including the FDA, and the NIH, and the patient representative organizations, and the patients who are very eager to contribute data, and they're very eager to contribute it under a good research protocol in scientifically acceptable manner that meets the accepted prospective standards for end-point-reliability assessment. We want to develop a largely patient reported but scientifically monitored database that's acceptable for the patients, the expert clinicians in the field, the NIH, and the FDA. And we are prospectively developing specific criteria for acceptance of all these measures by each party, so that everyone commits in advance to a rigorous protocol. We are going to obtain approval from all stakeholders for the items to be collected, and we will develop and gain approval for the levels of access to use of the database by the various stakeholders. And I think that can be done.

Then, if we go forward, we'll develop an efficient, modern, user-friendly website that will recruit Niemann-Pick patients and collect natural-history data. And we would like to enroll all patients, all [unintelligible] patients suffering from Niemann-Pick in this database. And I think that is not an entirely unrealistic agenda. Then we would tabulate the available small-end, clinical-design options that are appropriate for NPC and for rare diseases in general, review the key strengths and limitations of each, and develop and pursue the best possible design for a promising intervention for NPC. Now, I want to emphasize that while I think we can make some progress with small-end, clinical-trial designs, they are not a panacea. Under the current approach and under the mathematics of the small numbers for these diseases, even under the most flexible current FDA procedures and admirable work is being done here in the Office of Rare Diseases and Dr. Pariser's [spelled phonetically] group, but we do need to understand that [unintelligible] can be made with these innovative designs, even assuming that it would take decades, or I did a brief computation, even hundreds of years under our current procedures to develop

and test a modest number of therapies for every rare disease, which I think would be [unintelligible]. So, we can make programs with the designs for small end, clinical trials, but they will not get us to where we want to be.

So, given that, we have two proposals, and I realize that I am talking in very large terms here. I realize that this may ultimately need legislative action, which may be beyond the scope of this hearing, but given the previous speaker aside, it would seem that there's room for reinterpretation under existing statutes. And there are many, many proposals and a great deal has been done by many agencies, including the FDA, to improve procedures. So, I am offering some general remarks on a general direction that these might all be brought together under. We suggest that there be consideration given to creating a new investigational status, which would be something like a status for provisional administration during further evaluation, limited to interventions for rare, life-threatening diseases. And I think one would start with very rare diseases with very small numbers of cases. And then perhaps move on from there to the rare diseases, such as SMA, which have larger numbers, but are still rare by the official criteria. This would be, the idea would be to have carefully monitored evaluation on an ongoing basis. This would be explicitly experimental. These drugs would not yet be approved. There would be informed consent from patients on this basis. Patients, of course, are highly attuned to these considerations. And any qualified MD willing to accept the reporting responsibilities could administer such a therapy to a diagnosed and registered in some sense patient, and all this would need to be worked out.

So, experimental therapies with the new provisional administration [unintelligible] status would be serially evaluated and rejected and replaced until one is shown superior by conventional criteria. And this would meet the demand for the rigorous accumulation of evidence that I think we're not achieving at this point in a comprehensive way that we need to do for these rare diseases. So, this would allow a rigorous, closely-monitored, small-end, accumulating experiments beyond compassionate use, but for drugs, interventions which currently have less evidence than is currently required for full FDA approval. I think these could be ethical, and safe, and acceptable to patients in high-risk, small rare-disease groups. And it starts with very rare diseases, and by definition the number of patients would not be large for any disease that was eligible. And so these would be manageable projects. So, that's the first proposal to create a new investigational status.

And then, and many speakers, I'm sure, will speak to this, we do need to consider a recalibration of the risk-efficacy bounds, because it's currently appropriate for prevalent diseases but not for rare diseases. As it has been said and as will be said again, patients with fatal diseases, where no approved therapy exists, will accept more risk and uncertainty than those in other classes. And given this and given the small-end problem, statisticians are always dealing with uncertainty, then perhaps consider revising the risk-efficacy balance for this class of patients and diseases. And consider accepting an ongoing investigations, a probability of type-one error of or less than or equal to .102 sided instead of the conventional .05.

So, the conclusion is that I have advanced two separate, independent proposals. There's the issue of the extent of which they might require legislation or they might possibly, it

might be possible, to explore these under reasonable interpretation of existing statutes. But we applaud and are now committed to working with the FDA and the government agencies, but we do feel on the basis of our experience that change is essential to achieve the FDA mission and the mandate for patients afflicted with serious, very rare diseases. Thank you very much.

Timothy Coté:

Thank you Dr. Thompson. Do we have any clarifying questions from the panel?

Paras Patel:

Thank you. Next, we have Diane Muffett, please.

We will hear from Ms. Muffett and then from Ms. VanHoutan, and then we will -- oh, I'm sorry, Ms. -- yes. I'm sorry, what's your name again? We'll hear from Ms. Hickman, and right after we hear from Ms. Hickman, we will take a brief break, 15 minutes I believe, because we had one cancellation, so it'll make more time at the end.

Third Session

MDJUNCTION.com: Dercum's Disease Support Group

Teresa Hickman:

Good morning. I'm here representing the MDJunction.com Dercum's Support Group. My name is Teresa Hickman and I have Dercum's Disease. Because most people have never heard of Dercum's -- or Adiposis Dolorosa -- I'd like to describe our disease before I address the questions. Next page [inaudible]. Am I supposed to click it?

Dercum's Disease was first learned in 1888; 120 years later, there still has been no cause or cure identified and additional research is badly needed. We are fortunate to have one doctor who actively treats and researches this disease. She is the only one in the United States doing this. As you can imagine, it is very hard to get a diagnosis. We believe there are many more people who have not been diagnosed, as symptoms are multiple and varied. The primary characteristic is lumps or lipomas appearing on much of the body. The lumps are painful. Sensations of itching and burning accompany the growth of new lumps. Our symptoms seem -- other symptoms seen in Dercum's patients include overwhelming fatigue, muscle pain, and weakness, unwarranted weight gain, difficulty sleeping, and depression. The disease is progressive and often leads to limited mobility, disability.

The next slide shows examples of lipomas. The gentleman pictured there off to the left upper slide, he's swollen on his right upper arm. There can be swelling on one side of the body and not the other. Next to that is a picture of two that are visible and protrude out. Most of them however are within -- under the skin, so it's -- it can only be felt; it can't be seen. The woman underneath the gentleman has it -- she's got it underneath of her breast and on her upper ribcage. The little picture shows another lipoma, which is about the size of a moth ball [spelled phonetically]. If it's to the point where it's so painful it can be removed, the consequences are you're going to get five or six more back. There's a smaller one next to that one where she pinched it and you can see a little bit of it. Most

of them go from a rice size to anywhere from five to 10 pounds, but that's rare that it gets that big, but it will be removed if it does.

The woman on the bottom has it in her back, kind of, like, I guess they call it a buffalo hump, and the other woman -- and it kind of shows where you're kind of skinnier on the arm and then the fat grows up under the upper part of the arm. And the bottom picture off to your right is a woman who looks normally obese. She's got very much swelling around her knees and her ankle, but as you can see the lumps poking out are lipomatosis, and it is a very painful, painful disease.

Dercum's is a disease that goes against medical teachings. "Lose weight and exercise" is heard from many doctors. A paper published by Brorson and Fagher in 1996 reported that Dercum's patients often weigh 50 percent more than their normal weight. This weight is not lost by dieting. Strenuous exercise causes increased pain and often an increase in lipoma size or number. Lumps can be removed but it has been seen over and over that most grow back -- often in multiples. We don't respond well to traditional pain medicines like opioids, so it is difficult to stop the pain. We do exercise. It does hurt. Doctors don't understand that. We get so frustrated time and time again when a doctor says lose weight. It hurts to exercise. It increases the size of it, which causes the depression. You're depressed. You can't do things you used to do. You're depressed that the doctor doesn't understand, doesn't try to understand.

So, how do we treat it? We try non-traditional methods like Chinese medicines or we use medicines intended for other purposes such as cimetidine, statins, and aspirin. We search for treatment such as lidocaine infusions to stop the pain. We try equipment that uses microcurrent or gravity to ease the pain and alter the flow of lymph in our bodies. Most of these are not identified as treatment for Dercum's so are not covered by insurance.

Now that I've described what we face, I'd like to address the hearing questions. Question one: Orphan drugs are reviewed under the same process as non-orphan drugs. Our answer: Orphan drugs are often new and critical to the quality of life in those with rare diseases. Using an expedited review process for orphan drugs offers hope more quickly.

Question two: FDA uses an HUD to determine whether or not a medical device can be used to treat or diagnose a rare disease. Four thousand patients are needed to make an HUD determination. Our answer: 4000 is an unrealistic number in our case. There are less than 500 people with this diagnosis that we can identify on support groups, websites or blogs or who have visited our doctor. It would take 10 or more years to get 4,000 people, and we are suffering now. Our group would like to propose that new medical devices be tested on 100 patients and reviewed at the end of 12 months for any adverse effects. If none are found, the device should be approved with a caution that the test population was small. Let the patient decide if he or she wants to take the risk.

Question three: Current regulations for the approval of an HUD require a discussion of the scientific rationale for use and an explanation of why the benefit outweighs the risk taking into account probable risks and benefits of current devices or treatments. Our answer: Definitely we need to know the benefits versus the risks. However, we still have relatively few treatments that have proved to be successful. New devices and treatments

should be evaluated on their own without comparison. Again, we recommend using the sample group of 100 to make recommendations and to approve the use with a cautionary statement.

Question four: Comment on current processes for rare disease stakeholders to communicate with FDA regarding rare disease article development. Our answer: We applaud the use of patient representatives on FDA committees. We greatly appreciate that you recognize the value of the patient's perspective. We would like to see an increase in the communication about FDA processes and hearings. If our group wasn't a NORD partner, we would not have been aware of this opportunity. If FDA can broaden announcements or contact key members of groups representing the rare disease, it would be beneficial.

Now, I'd like to thank you for the time and your attention for getting our group the opportunity to share our perspective. Additional information about our group can be found at www.mdjunction.com/dercums-disease, and there you'll see the group leaders, Diane Muffett and Sylvia [unintelligible] and Chelsea. Does anybody have any questions?

Timothy Cote:

Thank you so much, Ms. Hickman.

Male Speaker:

I wanted to raise a point of clarification regarding the number of patients that you had mentioned with regard to the Humanitarian Device Exemption of the HUD. You had mentioned that 4,000 was the lower limit. It's not; it's the upper limit. So, there's nothing to prohibit specifically starting an investigative study into Dercum's and 100 patients, if that number seems visible for a researcher, that's something that should be pursued. There's no lower limit to the number of patients that can be [unintelligible]. The 4,000 is an upper limit at this time. Our question actually asks if the upper limit is appropriate or should it be raised to a larger number or not. Thank you.

Teresa Hickman:

Just to jump on that, I guess with that HUD which is a humanitarian -- I can't remember what that stands for at the moment, but it says that it refers to a small group, which is 4,000 or less, and usually, it goes into deeper [unintelligible] of with that being so small that's it's okay to do the research on a small number without having to do it as regular diseases, because it's just a small number of us right now.

Male Speaker:

The medical device regulations with regards to the types of studies and the necessary level of evidence for proof to get a device approved is different from that for drugs. The [unintelligible] probable benefit rather than safety and effectiveness. I think [unintelligible] presentation addressed specifically the drug issues, but in the device world, we talk about probable benefit, which is along the lines I think of what NORD representative was talking about, so we are with you on pursuing research in this area that gets to probable benefit for treatment of your disease.

Specific concerns with our questions are with regards to whether that probable benefit needs to be more carefully defined, and I think our statistical talk just before yours did discuss some of that, and we were eager to hear that.

Teresa Hickman:
Okay. Thank you.

Timothy Cote:
Again, thank you, Ms. Hickman for your experience. We move on?

Paras Patel:
Thank you. We will break, take a small break until 10:30. Thank you.

Timothy Cote:
At 10:30 we'll meet you all back.

Paras Patel:
Next, we have Tracy VanHoutan, please.

Forth Session

Batten Disease Support and Research Association

Tracy VanHoutan:
Good morning. I'd like to introduce myself. I'm Tracy VanHoutan from the Chicago, Illinois area. I'd like to start off by thanking the FDA for first of all holding these hearings and for also allowing me to present.

I'm the father of three children, two of whom were affected at Late Infantile Neuronal Ceroid Lipofuscinosis, more commonly known as Batten Disease. There I have a picture of my son, Noah, age six, and my daughter, age four. I'm also an active board member of the Batten Disease Support and Research Association, which is the largest organization in the world dedicated to research and support of Batten Disease family. I'm also the founder and director of the Noah's Hope Foundation.

So, what is Batten Disease? Imagine your son being born and develop normally until age two and a half, and then imagine one day his speech starts to regress and he begins to forget words that he had once mastered. Imagine your child who once played baseball and soccer no longer being able to pick up a bat or kick a ball. Imagine seeing over 100 seizures in two and a half years, and imagine your child having no known friends to talk about and never being invited to a classmate's birthday party. Imagine your child never being able to hug you and say, "I love you" ever again. Imagine a disease that slowly takes everything from a child, and eventually takes away the child. Imagine that this is not only happening to one of your children, but it is also begun to happen to one of your twin daughters as well. This is Late Infantile Batten Disease, and I don't have to imagine this.

Neuronal Ceroid Lipofuscinosis, also known as Batten Disease or NCL, is autosomal recessive. It is ultra rare, affecting two to four births out of every 100,000. Batten Disease is actually 10 different disorders with different defective genes, and the children, as I've stated earlier, develop normally until age of onset, and then begin to regress. It's characterized by accumulation of waste material to the brain, and some of the symptoms you begin to see are vision loss, ataxia, seizures, loss of motor function. This disease is always fatal. In the late infantile form that affects my two children, life expectancy is eight to 12 years old. And currently, there is no FDA-approved therapy for Batten Disease.

Here are a few of the children that I have met in the last year that are affected by Batten Disease. The first girl here is Taylor from North Carolina with the infantile variant form. Next is Mary Payton, from Louisiana, Hayden from Wisconsin. The next boy here is Jasper, also from Chicago, Illinois, with the late infantile, the same as my son. Next is Christiane from Texas. She has a juvenile onset and was detected very early, as her father is in the biotech industry, and I'm going to talk a little bit more about a project he's working on.

The next few pictures should stand out. This is Amber, Sara, and Sandy, sisters from Illinois who've all lost their battle with Juvenile Batten Disease in the last year and a half, Sarah and Sandy within two days of each other, a few months back. As this disease is autosomal recessive, it often strikes more than one child in a family, and in this case, every child in the family. Next we have Bridget, also from the Chicago land area, suffering from the late infantile form that my children have. And the last young man here -- a very few of you in the room may recognize -- his name's Daniel, from California. Daniel passed away suddenly a few months ago and he also had the late infantile form.

I'd like to take a minute just to mention several of the other foundations who are working hand in hand with to find a cure or treatment for Batten Disease. There's our national foundation, the BDSRA, Beyond Batten Disease Foundation, Our Promise to Nicholas, Taylor's Tale, Nathan's Battle, Hope 4 Bridget, Hayden's Hope, and the Mary Payton's Miracle Foundation.

So, let's talk a little bit about how Batten Disease is diagnosed. In years past, retinal exam and MRI were useful, but only if a physician recognizes the signs of Batten Disease, and let me tell you, after visiting over seven neurologists in different cities around the country, they don't recognize this. Skin microscopy was also a useful diagnostic tool. They're currently enzyme testing for the infantile and late infantile versions, which are both [unintelligible] enzyme [unintelligible] has become more readily available, but it is only performed at one hospital in the U.S.; that's Seattle Children's. Gene sequencing is also becoming more common, with the majority of the testing being done at Massachusetts General, and soon we hope to have universal carrier screening using next generation sequencing. This is being done in partnership with the Beyond Batten Disease Foundation in Texas -- I showed you a picture of Craig's daughter on the previous slide -- and the National Center for Genome Resources. They are developing an inexpensive -- that's less than \$500 -- test panel for over 450 rare genetic childhood disorders. Current hopes are that this test will be available at the beginning of next year

and that the costs of that test will continue to decline. Our future goal here is obviously the early diagnosis leads to improved outcomes, eventually, for Batten Diseased children.

[unintelligible] get to potential treatments for Batten Disease. Currently, we are looking at four different approaches for Batten Disease. We have gene therapy, which has completed a phase I trial and is now looking at starting a second phase I trial, stem cell therapy has completed a phase I trial and has an application to the FDA for phase II. Direct enzyme replacement is being considered and small molecule therapies are also being explored, [unintelligible] neuro, reduction of neuro-inflammation in the late infantile and infantile versions. We're also beginning to look at [unintelligible] mutation therapies as well as chaperone therapies.

Well, there has been some progress in developing treatments, and for this we are grateful for the efforts of researchers, private foundations, the FDA, and the NIH. There is currently one project under review with the FDA, as I stated previously, two projects currently recruiting patients, six projects in pre-clinical or proof-of-concept stage. These projects offer a very small amount of hope to children currently with diagnosed children [sic]. If they are delayed or not well understood at the regulatory level, then we could lose another generation of Batten Disease children. It is one thing to sensitive to the needs of patients with rare diseases, as we believe the FDA is, but we also believe that people specifically trained in genetic medicine should be making decisions for treatments for rare genetic disorders.

The next two slides describe some of the challenges in developing treatments for Batten Disease. First of all, it is a difficult disease due to the neurological problems and blood-brain barrier problem that needs to be overcome. It is hard to measure neurologic decline in young children with variable rates of progression and variable degrees of reversibility in the disease. Clinical neurologic endpoints for studies are imprecise and varied in their accuracy. Continuing on to some of the challenges, the drug development has been hampered by the nature of this difficult disease. We find that the neurologic damage is not likely reversible and that most patients are not diagnosed until they have neurologic disease. The clinical endpoints may be too late to allow assessment of a drug effectively. The populations are small and variable and these diseases have limited development of treatments, and if we do find a drug that works, will we be able to prove it?

So, let's talk a little bit about accelerated approval regulations. These regulations were designed to assist in the early approval of drugs that have a clear effect on marker of disease. This avoids the problem of waiting until a patient dies or in using imprecise clinical measures that may block or eliminate investment, yet only one genetic disease has been approved via these regulations. Why is this? Access to the accelerated approval regulations is needed for Batten Disease. A measure of brain injury should be sufficient to assess whether a very early stage baby is being improved. Given the high morbidity and serious outcomes, clinical endpoint-driven studies would be difficult to do. The rarity and lack of other clinical data presents Battens and other neurogenetic disorders from accessing the accelerated approval pathway. We must treat these diseases before it has neurological effects and this pathway is not available for the diseases that need it most, which surely cannot be what Congress intended.

Rare and devastating neurogenetic diseases like Batten Disease need access to accelerated approval. Our kids -- and my kids -- have a 100 percent probability of dying with Batten Disease. We need to figure out how to allow markers of brain injury to be used to study new treatments in these small numbers of patients. Allowing access to accelerated approval will hopefully spur more investment in the difficult to study diseases, like Batten Disease, and many other like it. We need survival to be better than zero percent.

I'd like to end with two recommendations from the Batten Disease Support and Research Association and Noah's Hope. The first recommendation is to establish a new office of drug evaluation for biochemical, and genetic diseases. We would hope to add experienced staff with appropriate genetics expertise to this panel, have them focus on disease areas not well covered today. We also ask them to establish guidelines for rare and ultra rare diseases and help to improve coordination between university researchers, non-profits, private companies, and NIH to assist in translating research to patients.

A second recommendation is to establish protocols allowing the use of surrogate endpoints, specifically qualifying neurological endpoints that would change the dynamic of clinical trials and assist with the development of treatment. There are no FDA-approved biochemical endpoints or markers of neuro-degeneration at this time. We believe that surrogate endpoints would not replace clinical outcomes, but would serve as supplemental endpoints of treatment of disease. Surrogate endpoints hold great potential for approval in clinical trial design for ultra rare diseases, and we believe that they would lead to the acceleration and development of new treatments for patients with no other alternatives.

Thank you for your time. Are there any questions?

Timothy Cote:

Thank you, Mr. VanHoutan. Do we have any clarifying questions from the panel?

Paras Patel:

Thank you. Next, we have Mary Gustafson.

Fifth Session

Plasma Protein Therapeutics Association

Mary Gustafson:

Thank you. I'm Mary Gustafson. I'm vice president, global regulatory policy for the Plasma Protein Therapeutics Association. I would like to thank FDA for organizing this hearing to explore the review practices of the FDA as they relate to therapies to treat rare diseases.

PPTA is an international trade and standards-setting organization. We represent the collectives of source plasma, which is the source material in the manufacture of plasma protein therapies, and we represent the manufactures of plasma-derived therapies and their recumbent analogs, collectively referred to as plasma protein therapies.

Plasma protein therapies are used in the treatment of a number of rare diseases, most often to replace missing or defective plasma proteins in the patient. The disorders treated are often genetic, chronic, and life-threatening or life-altering. The disorders include hemophilia and other blood clotting disorders, immune deficiencies, and hereditary emphysema. The disorders require the patients to receive regular infusions or injections of the therapies for the duration of their lives.

Among the companies that manufacturer therapies for rare disorders include Baxter BioScience, Biotest, Cangene, CSL Behring, Grifols, Kedrion, Octapharma, and Talecris.

FDA stated the purpose of this hearing in an April 30 Federal Register notice. Included in the notice was the request to respond to four areas of concern. The one that relates to our members is number one, which states that FDA reviews orphan drug marketing applications under the same review process and standards as drugs for non-orphan indications. FDA has requested comment on whether this practice has adequately addressed the needs of patients with rare disorders and further requests suggestions on improvements to the review process.

First and foremost, PPTA appreciates the agency's willingness to review current practices to see if improvements are warranted to move forward the goal of providing therapies to patients with rare disorders. Review this opportunity as a part of a paradigm shift over the last several years, going beyond the review of a drug for an orphan indication to view it in the review as part of the over-arching goal of providing therapies to patients with rare disorders. PPTA member companies manufacture therapies that are reviewed as biologic license applications within the Center for Biologics Evaluation and Research, specifically within the Office of Blood Research and Review.

In June of 2005, CBER sponsored a public workshop entitled "Biological Products for Treatment of Rare Plasma Protein Disorders". The workshop provided the opportunity to exam the role of the regulator and they're only [spelled phonetically] reviewing applications presented to them for orphan indications, but also in being a partner in advancing the development of therapies for people with rare plasma protein disorders. While a first step, it was an important step. Not only were manufacturers provided an opportunity to present, but also patients and academia were heard, as well. We're pleased with the progress the agency has made since the 2005 workshop. Recent approvals have demonstrated the agency's progress in adapting novel approaches to the review and approval of therapies to treat rare plasma disorders.

While good progress has been made, we would like to see the result and strides formalized in consistent guidance, very similar to what NORD has recommended, and also harmonized internationally. Plasma protein therapies are marketed globally for the treatment of small patient populations. Even on a global basis, they're small. Our most important goal is to have harmonization across different regional regulatory bodies. Harmonization is not really the right word; anyone can harmonize. Harmonization simply infers that the most stringent requirement is met and used universally. A more appropriate term would be a global regulatory strategy. In order to accomplish this, it requires international regulatory bodies to communicate and work together -- and we

know this is happening more and more -- to develop requirements that are compatible with each other and recognize the unique issues that occur when developing policies that affect a finite patient population with a lifelong need for treatment. Some of the challenges include harmonizing the differences in the number of patients needed for the study and the recognition that this finite group of people may be subjects for several studies during their lives.

Some of the treatments considered for marketing in the U.S. have been available for years in other regions. In order to bring the therapies in the U.S., there's a need to consider studies that were performed outside of the U.S., sometimes years before, and not under U.S. IND requirements. Obviously, this presentation was prepared before last week's release of the inspector general's report highlighting concerns over U.S. approvals based on foreign studies. While I have not had a chance to study this report in detail, I hope that its existence will not cause U.S. regulators to circle the wagons nationally, but to view this as an opportunity to reach out further to provide assurance of oversight, not by thinking that the U.S. can go alone, but by partnering with international regulators and leverage all resources in setting standards in inspections and in training and education.

Areas that need attention and a global regulatory strategy include the requirements for the clinical trial and clinical design. Is a double-blind placebo controlled trial really the gold standard in rare disorder therapies? Use of one-arm [spelled phonetically] studies, historical controls, registries, and other novel approaches must be considered. These may be adaptive clinical trials or a more effective use of phase IV studies and pharma co. vigilance in the U.S. and globally.

The size of the study is always an issue when the size of the population being targeted is small to begin with and many have been subjects in numerous studies already. This leads to problems in recruitment of subjects; there simply aren't many to begin with, and even fewer willing to participate. Compliance is another issue. The patients with the rare plasma protein disorders don't require treatment for a short time; they require treatment for the duration of their lives. They should be active participants in determining their enrollment, participation, and compliance. Education should be a two-way street. The regulators can impart to the patients their regulatory needs, but the needs of the patient should also be considered in determining why and how the patient should participate. In fact, they are the experts living with their disorders. Endpoints of studies should be carefully evaluated in terms of what is required pre-approval and what can be gathered post-approval in phase IV or through surveillance. Surrogate endpoints and biomarkers should always be considered, although we recognize that there is more work needed to identify appropriate markers and develop and standardize assays for those markers; perhaps this would be a topic for a workshop.

The development use of patient registries, ideally, on an international basis, is of vital importance in the development of therapies for patients with rare disorders. Currently, patient registries appear to be used to identify patients for possible recruitment and safety monitoring, but not efficacy. I don't have the answers, there's a lot of information out there, but it does seem that more could be done with data collected and registries. Perhaps this would be another workshop topic: to examine existing registries and develop best practice models to be used for efficacy determinations, as well as safety in the future.

In terms of manufacturing therapies for patients with rare disorders, the realities of a manufacturing scenario should be considered. While no one would advocate a different standard for good manufacturing practices, the fact that some of these therapies may have been developed some years ago, are manufactured less frequently than other drugs, and have been validated on equipment and procedures that are not cutting-edge must be considered. As new requirements are put in place for process validation and “current” good manufacturing practices, the special manufacturing characteristics of these therapies must be considered in order for them to remain viable marketing options for the manufacturer.

PPTA thanks FDA for holding this public hearing in recognizing the uniqueness of developing therapies for rare diseases. PPTA looks forward to continuing to work with FDA on these important issues.

Thank you.

Timothy Cote:

Thank you, Ms. Gustafson.

Paras Patel:

Thank you. Next, we have Sheryl Harris please. Ms. Sheryl Harris?

-- I have Mary Schluckebier on the Celiac Sprue group on my agenda.

Paras Patel:

Okay, if Ms. Harris is not here, next we'll have Jonathan Jacoby, please. We have anybody here from the Rare Disease Advocacy Research Education? He's here?

Sixth Session

Rare Disease Advocacy Research Education Sun Valley Pharma Consult, LLC

Jonathan Jacoby:

Thanks very much. My colleague, Ron Browne, is somewhere between Australia and the NPS meeting there and Washington D.C., so I'll be a little briefer than we might have been otherwise. Thank you very much for this opportunity; very much appreciate it. The R.A.R.E. Project work with patients and patient advocate groups to raise awareness and build resources in order to help fuel the accelerated development of therapies for rare diseases. Given the fact that Dr. Browne is not here, I'm going to focus on examples where patients and patient participation have enhanced or can enhance the movement for clinical trials.

So, these are the topics that we're going to cover. I won't read all my slides and bore you with them, but you can see these are the -- basically the case studies that we're going to be dealing with on the topics, and then we're going to reinforce the suggestions presented by Dr. Thompson, by NORD, and maybe suggest a couple of additional strategies.

All right. Slide doesn't want to move; there we go.

The case studies will be in these five different areas, five different diseases and disease groups of which we've worked. So, the first one is Niemann-Pick Type C. As Dr. Thompson has told us, Niemann-Pick Type C -- I am the father of a child with Niemann-Pick Type C as well -- is an autosomal recessive fatal disease, estimated 500 cases worldwide. A group of parents and researchers got together about three years ago to create a collaborative effort in order to try and advance Niemann-Pick Type C research, and they and others have identified a number of promising needs and compounds.

You can see some of them here; you're familiar with NAC and curcumin. I think FDA is quite familiar with Miglustat or zavesca, which is still not to be approved -- still not been approved by FDA but is being used off-label by about half of the patients in the United States and probably would be used by more if insurance would cover it. Gleevec is another off-label drug or drug being used off-label based on mouse studies. Recently, two patients in Oregon have begun treatment on Gleevec off-label. There are number of repurposed compounds; you'll hear extensively a little bit later about cyclodextrin, so I won't spend too much time on it now, but just let me mention that there are also a number of new chemical entities in the pipeline. Many of these have been developed based on active participation of parents with researchers in trying to move the process forward.

With regard to cyclodextrin, the discovery of cyclodextrin was serendipitous, at least in terms of its efficacy for Niemann-Pick C in the animal model. In a little over a year after the discovery, that it is capable of doubling the life expectancy of mice lacking the NPC gene, individual INDs were filled with the FDA to initiate IV infusions in two identical girls, twin girls. Recently, the sponsor of the INDs, Dr. Hastings [spelled phonetically], with the help of Dr. Browne, fought successfully for orphan drug designation, and you know that very successful workshop out in Claremont [spelled phonetically] led to that. In fact, the scientific interest in cyclodextrin is so great that it was highlighted as part of a two-day workshop sponsored by the NIH just last month.

I think the point that I want to make here is that because of patient and parent participation -- not only pressure, but actual participation in the process -- movement toward the clinic has been accelerated. There are a number of issues that still need to be resolved. I don't want to go into detail with them, but there are many more penetration [spelled phonetically] of the CNS, there's a need to extrapolate the unidose [spelled phonetically] from the limited animal studies; all of these are within the realm of possibility, but need to be accelerated.

SOAR has also sponsored a good deal of research related to biomarker development. This is a good example of how parent-initiated activity, such as measuring various blood markers in NPC children, has helped me to randomize controlled clinical trials, based on the findings of the NIS observation study that NPC children have low levels of glutathione and elevated oxysterols. The parents were able to obtain age matched based on blood samples in order to validate the differences between the control groups and the diseased children, and based on these findings, Dr. Porter at the NIH filed an IND to test

whether the glutathione precursor and N-acetyl cysteine, NAC, is capable of altering these biomarkers.

Another good illustration of the collaboration between parents, academics, scientists, and the NIH is that a 30 patient crossover study was completed within one year, or is just about to be completed within one year. For a disease like NPC with so few available patients, it's truly a testament to a successful collaboration between stakeholders. There's still a very great need with a disease like NPC, Batten, and other progressive neurological diseases foreseen as biomarkers. This is one of the greatest challenges that is being faced, and unfortunately, as soon as people mention CNS, it seems to scare people away, which from the perspective of a parent who has a child with a neurological disease is too bad, because we know that unless we can get to the CNS and start testing the CNS, our children's lives are at great risk.

Case number two is a case from a previous experience with Creutzfeldt-Jakob disease which I just want to mention, because it's interesting, again, in terms of what it shows in terms of the participation of patients, or in this case, the patient's family, in the process. A California man who was diagnosed with this incurable disease five years ago lived about a year and a half longer than anybody expected him to live, and that's largely because his family members discovered that Prograf -- which is a medication not originally developed, as you probably know, for CJD -- could be effective with CJD, and despite the efforts of many others to identify treatments, nothing worked except for this one particular drug that his family members found. Unfortunately, these learnings were captured only for the family and by the physician; they were not cataloged or broadly disseminated, and as a result, it was a lost opportunity to build from this experience.

Case number three is Sanfilippo syndrome, or MPS III. As you know, MPS society is the central agency for funding research and supporting families with children who have MPS disease. There are a number of patient advocate foundations, including Team Sanfilippo, with which we have worked. Based on our work with the scientists, industry, and Team Sanfilippo to further discover research, we believe that initiating patient-driven observational studies similar to the NIH observational study in NPC will advance clinical trial in the future. And there are a number of these trials that are already either underway or being contemplated. Shire has a natural history study in MPS III A for their intrathecal ERT study, there are foundations in Europe that are preparing gene therapy for small trials, and biotech companies with small molecules on the horizon. Literally all patients with Sanfilippo disease are taking the over the counter nutritional supplement Genistein because animal findings suggest that it can reduce urinary GAG levels. Unfortunately today, there are no well-controlled clinical trials regarding this compound. An opportunity exists to implement the sort of patient-driven studies described by Dr. Thompson for this condition, and specifically this case.

Case number four: biotin deficiency. This was Dr. Browne's experience, so I'll just read what he sent. He had an interesting experience with FDA about 10 years ago when he was working for a company that had been providing the amino acid L-5-hydroxytryptophan to patients with biotin deficiency. The amino acid acts as a co-factor and is essential for these patients. The company had been providing the product to 12 patients for about 10 years. Dr. Browne filed an orphan drug designation for the

product and met with the FDA. FDA was willing to consider the new drug application based on patient narratives along with chemistry manufacturing control section. Unfortunately, the pharmaceutical company decided not to file the NDA due to business reasons, but the example illustrates that for some rare diseases, FDA was willing and has been willing to work with the sponsor to consider approval without well-controlled studies which would have been impossible to conduct with so few patients.

And then case number five is Huntington's disease. We've been working with the Huntington's disease Society of America on the question of clinical trial recruitment. There's a robust pipeline of potential therapies, which is the good news. The bad news is there are significant barriers to participation in trials; the cost, or the perception of cost; protocols that are considered by many patients dissenting; the, again, patients who consider functional relevance to have essentially be irrelevant to their personal situations; difficulty with site access; and psychological factors. As a result, there's a risk of insufficient enrollment for these very, very promising trials. What we have done in this case is to meet with the patient population to develop strategies with them for recruitment for clinical trials, including a virtual consumer service back-end, a community education program modeled on the Midwest Academy, and mobile clinical trials for those who are in remote areas.

So, briefly, I want to just share with you some options and recommendations for small, patient-driven clinical data generation as a pathway to regulatory approval of orphan drugs. You're quite familiar with these current realities -- I won't go in to them again -- and you're very familiar, again, with the options available for rare disease patients. Let me just say here personally that we not only appreciate that you take the time to listen to us -- I say this as a father -- but we have great expectations that the -- when we say things like, "We need greater flexibility," that you really hear what we're saying, that we're not just repeating policy statements in fact, but that our children's lives, and in some cases, our own lives are at stake, and the need for flexibility, the need for innovation, is of critical importance, not in a matter of years, but in a matter of weeks and months.

You might ask, why is it so important for the FDA to take official action about some of these things. I'll speak to the case of Zavesca. My son is on Zavesca; he doesn't need the FDA to approve it in order for him to take it, and luckily, we have an insurance company that's willing to pay the price; however, I have too many children whose families cannot get Zavesca because of their insurance policies, and I also know that the chances that Zavesca works in some way are much, much, much greater than whatever minimal risk there might be with Zavesca; and therefore, getting marketing authorization is critical so that insurance companies can pay for this, so that individual INDs for experimental therapies cannot be considered to be so prohibitively expensive. And in the case of over the counter products like Genistein, the absence of prescribing information makes the use of these products very difficult

I want to make just one sort of general comment here about the value and the importance of patient involvement and the kind of feedback and input and activities that we conduct here. When I was first faced with this horrible situation of having a child with a rare and fatal disease, the geneticist with whom we met said, "Don't look on the internet, you're not going to find anything. Support that local patient advocacy group, support the

research,” and although he didn’t say it, but what he really meant to say was, “We’ll take care of the rest.” In this day and age, that’s just not possible. For those of us who have been out in the world and know what the power of the internet is and know what the power of engineering is and know what the capacity and the potential that we have as individuals, we’re going to look. However, if we look and we act without guidance and without the collaboration and participation of agencies like FDA of the sort that you are exhibiting today, then the fuel that we expend is going to be spilled into -- something like the Gulf of Mexico. It’s going to be not just wasted, but it might actually be damaging. So, we are not going to slow down in our efforts to innovate and to advance; what we need from you is guidance and partnership at the same pace that we are moving, and believe me, we’re going to move as quickly as we can.

So, this is just a slide that essentially reinforces the recommendations made by Dr. Thompson, to whom we are quite grateful, and we have a number of diseases that are waiting in line for recommendations like his to be implemented; I won’t go into detail about them, again. I will say that a lot of attention is being focused on biomarkers which hold promise as surrogate endpoints, and it should be noted that it’s easier to collect blood and even CSF at local hospitals than at centralized locations. So, again, the possibility of global flexibility and more innovative thinking about the location and the structure of these trials would be very beneficial.

Here’s just one possible mechanism for non-traditional orphan drug approvals; I’ll go through it very quickly. The first step is to obtain orphan product drug designation, after which stakeholders can start awareness of the opportunity utilizing the foundations, clinicaltrials.gov, et cetera. Individual investigator, IND documentation can then be made readily available on the Web. The preclinical safety and efficacy data requirement needs to be minimized; in other words, flexibility, again, is key. It is also key to get FDA and NIH buy-in for open access and HIPAA-compliant database. Very important that patients should have access to this worldwide, given the fact that the Web can now help us reach out to other countries seriously. Observational, safety, video, biomarker data can be entered by individual investigators, INDs, and/or by the patients themselves. After 12 months data from a relatively small percentage of the U.S. population, it should be possible to move towards regulatory approval. Again, this is just one idea that quite frankly only a few people came up with. The possibilities for a group like this getting together and brainstorming and coming up with a plethora of other ideas are endless.

So, finally, what’s needed, again, that NIH and FDA agree on open access Web-based data capture technology and hosting, that we have more disease-specific assessment tools, more disease-specific biomarker assessment, more funding, and more attention paid to helping to facilitate patient involvement.

Thank you very much.

Timothy Cote:

Thank you, Mr. Jacoby, for your contribution.

Paras Patel:

It looks like we had a few speakers who were not able to join us today, so we'll be breaking early for lunch. If you're exiting the building, please exit via building one and enter --

Timothy Cote:

Oh, I'm sorry, I think that the Celiac -- great, you're back.

Paras Patel:

Oh.

Timothy Cote:

Welcome, please.

Paras Patel:

Welcome.

[low audio]

Timothy Cote:

It's okay.

[low audio]

Oh, yes, yes, yes. Please, you are?

Sheryl Harris:

My name is Sheryl Harris.

Timothy Cote:

Sheryl Harris.

Sheryl Harris:

[Inaudible]

Timothy Cote:

Please take the podium, Ms. Harris.

Sheryl Harris:

I broke my toe [unintelligible] --

Timothy Cote:

Oh, you broke your toe, so please do sit down then. Okay.

[laughter]

Sheryl Harris:

I apologize for that.

Paras Patel:
And you have a clicker.

Seventh Session

Celiac Sprue Association

Sheryl Harris:
Thank you. Oh, I have a clicker.

Is this the one that it was replaced? Is this the final one? Okay. I guess there's a technical snag on this one.

So, my name is Sheryl Harris and I'm a registered dietician and nutritionist from Alexandria, Virginia, and I'm delighted to be here today and so delighted to have this opportunity to present on Celiac disease and medications. And I'm representing the Celiac Sprue Association, which is the largest non-profit in the United States representing people with Celiac disease.

And so...A little about Celiac disease: Celiac disease is an autoimmune condition that affects the small intestine, affects the villi of the small intestine, and essentially, when someone has Celiac disease, the intestine is destroyed and people can't absorb any of their nutrients properly. The bad news is that there's no cure, there's no magic bullet, there's no medication, but the good news is that there is a solution, and the only solution available is life-long adherence to a strict gluten-free diet. And so what that means is no wheat, barley, rye, or oats. And it means no wheat, barley, rye, or oats in foods, and it also means no wheat, barley, rye, or oats in medications. And it means none; when you say no, it means none whatsoever. So, not if it's your birthday and it's your birthday cake, not at a wedding, not just shaking crumbs off of something, it means absolutely strict adherence.

Oh, these are things -- I'm sorry about that. Okay, so when people are diagnosed early, the prognosis is pretty good; things do work well as long as they are very strict. The people who end up having health issues are the people who are not able to strictly follow the gluten-free diet. And so, the risks of Celiac disease, cost-wise, are absolutely huge. The risk of cancer, the risk of miscarriage, the risk just of health care costs overall, and that's not even looking at the emotional and physical drain on someone in having a disease that in many cases is very painful and is very debilitating. The data that's out there suggests that it takes people seven to 10 years from when symptoms start to getting properly diagnosed, and I'm sure that these numbers are starting to go down over time because of the greater awareness of Celiac disease.

Okay, so the only possible risk-free choice for Celiac disease is absolutely no wheat, barley, rye, or oats. So, even a milligram, even a crumb of gluten is enough to cause the inflammatory autoimmune process in your body. So, it's something where the only way to do it is to be as strict as possibly possible. And so, once people are diagnosed, they're essentially on their own to manage the diet, and obviously, the goal, as with everything,

is to live and to be as well and to be as healthy as possible.

And diagnosis of Celiac disease is pretty challenging, and it's pretty challenging for a couple of reasons. When I was in school, which wasn't very long ago, what we were taught was that people with Celiac disease, it was the two or three-year-olds who wasn't gaining weight and had the big, distended belly, and just very young children had Celiac disease, and it was very uncommon. And I can say now that I have clients who are diagnosed with Celiac disease in their 80s. Some were underweight, some are overweight, across male, female, socioeconomic class, age, different ethnicities; everyone, you know, a variety of different people do get Celiac disease. And so that's part of why diagnosis has been so challenging because our old views really no longer serve.

So, when you think of Celiac as a gastrointestinal disease, or historically it's been thought of that way, but a third of the people diagnosed with Celiac now have absolutely no gastrointestinal symptoms, which is why it has been so hard to diagnose and is currently. And, refractory I and II sprue is basically when people have had the disease for a long time and haven't been diagnosed or aren't compliant with their diet, often they reach a point where even the gluten-free diet isn't enough to help them. And so that's why early diagnosis and strict treatment is absolutely critical.

And so, the symptoms that people have when they are diagnosed are quite varied, but none of them are very much fun. You got chronic diarrhea, joint pain, abdominal pain, fatigue, constipation, asthma, type 1 diabetes, osteoporosis, small -- peripheral neuropathy, which is nerve pain. A lot of these conditions are quite debilitating, and there are actually hundreds of others, from headaches, to skin conditions, to all sorts of other autoimmune conditions that do accompany Celiac disease.

As shouldn't be surprising, many of these conditions are things that we take medications for. And that's why having medications that are safe on a gluten-free diet for someone with Celiac disease is absolutely vital.

Whoops. Back.

Okay. And so, when we say that someone with Celiac disease cannot ingest any gluten, that's including medications as well. At this point in time, if we were to -- if someone went to their doctor and were prescribed, say, penicillin, they would get a thing of pills and it would say penicillin in X number of grams. What it wouldn't say is what kind of filler was used, what kind of excipients, what kinds of things are used in the coating. And granted, the amount of these ingredients is quite small, but for someone with Celiac disease, this is absolutely vital and it's enough to sabotage their health. So, at this point, this information isn't readily available on any kind of labeling or in the physicians' PDR. So, at least with brand name drugs, often you can get this information when you call, but I can say as someone who's called myself when I've been sick, sometimes it's taken me 48 hours to get an answer, which when you're sick and you immediately need a medication, it just doesn't work. And, some of the times that I've called, I've been told that I'm getting this information because I'm a health care professional, whereas they say

specifically that it's their policy not to share the information with the patients themselves. So, obviously this gives huge barriers who need this information.

Generic drugs are even more challenging, and the problem with that is with generic drugs, they're using what's least expensive at each point in time. So this week, maybe corn starch is least expensive, next week, it may be wheat starch, the week after, tapioca. And so, there's no sense of what is always used as a filler, and especially for people who aren't fortunate enough to have many drugs covered and many medications covered by their insurance companies, the cost of brand name drugs can truly be prohibitive.

And now, order medications can also be a special challenge because there isn't any way to specifically ask all the questions so that people can make sure that they're getting safe medications. So, the recommendations by the American Society of Health System Pharmacists are very clearly advocating that manufactures declare the name and the derivative source of all excipients on the labels, so if it's from wheat starch it says it flat out. And this much more beneficial than just a vague idea of, "Yes, it has gluten; no, it doesn't have gluten." What we'd like and what would be most beneficial is a sense of what really is in these medications. And not only can that help people with Celiac disease, but I'm sure there are other allergy groups and other things like that can also benefit from this vital information.

And one of the other things is that it's not just medications that are affected. Since Celiac disease is a disease that affects every system in your body, other medications and other medical treatments are also affected, and one example of this is vaccines. So, when children who have Celiac disease who aren't treated are given vaccines, like hepatitis B vaccine, for example: over half of them don't actually get immunity to the disease. And according to CDC recommendations, all children should be receiving this vaccine, and yet one New York study showed that over half people didn't actually get immunity; another study showed that 68 percent. So, this is really huge because these kids grow up, they go to school, and when children go to school, they're asked what immunizations they received, not how effective they were. And when these children grow up and work in hospitals or in nursing homes or in other health care facilities, again, we're basically looking at what shots did you get, not how effective were they. So, that is really something that's absolutely vital, that people are aware of these things because the population impacts are potentially huge. So, some places, like Israel, is working on a different kind of vaccine that circumvents the issue and will work for children with and without Celiac disease. Boosters are some things that can be helpful, but it is an important and vital piece to look at. And that's the clinical trial in Israel that's underway at this point.

And so, last but not least, in some ways, we belong here, and in some ways, we don't. Celiac disease is in some ways a rare disease in that it's rarely diagnosed; one percent of the population has Celiac disease -- one percent of Americans have Celiac disease. And yet, according to the University of Chicago, 97 percent of those people are not diagnosed, and so the number of people who are diagnosed is quite rare, whereas in actuality it's a huge chunk of the population. And so, the FDA, in considering this legislation to work on medications and to work on clear labeling, really has the power to impact the lives of a huge number of people in this country in a really large way. At this point, foods are

labeled for at least the common allergens, so at least wheat is labeled, and many more and more companies are putting the information on their packaging, whereas people often don't realize that medications aren't labeled the same way, and oftentimes, their doctors don't realize either, which puts a large gap for people who the only treatment and the only way to stay safe is to strictly manage the diet for their entire life.

And so, I truly hope that you'll be able to consider doing something so that the health and safety of people with Celiac disease is ensured. Thank you so much for your kind attention.

Timothy Cote:

Thank you, Ms. Harris. Okay, I think we're ready for a lunch break. Paras, what's the timing on this?

Paras Patel:

Yes, we will be breaking for lunch, returning shortly before 1 p.m. There is food facilities available outside for purchase. If you are leaving the White Oak campus, please exit through building one and return through building one. See everyone at one o'clock. Thank you.

Eighth Session

Kakkis EveryLife Foundation

Paras Patel:

Okay. Good afternoon. We're going to go ahead and get started, please, if everyone could have a seat. Next, we have Emil Kakkis presenting, please.

Emil Kakkis:

Good afternoon. I want to thank the committee for having me speak today, and I hope to give you a perspective, and Dr. Cote, and Dr. Meal [spelled phonetically], and Dr. Paras, you've all heard this before, so I apologize for some of the repetition. But I want to hopefully put forth what my experience in drug development has said about what are ways that we can practically and efficiently improve the rare disease review process.

After about 11 years of BioMarin and a total of 18 years of drug development, I started a foundation this last year to focus on these efforts and to try to do, from what I've known, what could be improved, and we came up with the CURETHEPROCESS Campaign, which is really focused around three goals. Now, I want to point out that there are many things that you could try to improve, but we focused in on three which we thought were approachable, practical things which could be done that would make the process better.

The three goals here: establish a new Office of Drug Evaluation, this is about specializing the review process and continuing to add additional expertise to the existing expertise, and there is significant existing expertise at FDA, but also letting that group work together as a [unintelligible] over time. We also believe in improved accessibility of accelerated approval pathways are important; I'll talk more about that. And the third area was trying to improve study designs and statistical analysis methods to try to get the most

power out of relatively difficult small studies, which are a great challenge and are often really need to be different for what we do in large market disorders.

Oh, boy. Not working. There we go.

So, our campaign is formally endorsed by 129 organizations; we had an 11 addition between the times these slides were submitted, and we continue to get support both from patients who are involved in a lot of rare disease projects, as well as from physician organizations like the society for neuro-metabolic disease and the American College of Medical Genetics.

Oops, all right.

So, we know rare disease treatments are being developed and have been successful, and Dr. Goodman [spelled phonetically] talked to them recently at the congressional hearing; certainly a number have been developed for genetic disorders, so we don't deny that. The process can work for a number of diseases, particularly if they're large enough and there clinical findings are immunable [sic] to treatment. In the standard paradigm, certainly drugs have gotten approved, but what the problem is that there are a number of diseases where the paradigm doesn't work as well, either because they have difficult biology like neurological disorders or bone disorders, where they're just so rare that there's not enough market incentive for the investment. For those situations, the process may not work as well, and those are the ones we're really trying to focus on. So, we don't doubt that there are good drugs getting developed, but we do need to do more for some of these other sources that are not getting treatment.

And the one example I bring up commonly is Sly Disease, or MPS VII, and this has been successfully treated in animal models since 1993. And there's only about maybe a couple hundred worldwide with this disease, but clearly, enzyme therapy in an MPS disease -- I don't think anyone would deny that's likely to work in humans since there are already three approved products for other MPS disorders. You know that's going to work, but who's going to develop it for that small of a market? But it could be done if there's an accelerated approval pathway for it; it might be doable with a single trial approach. That's not something that's been allowed recently. It depends on the disease having examples, maybe the one that was mentioned earlier: the RAGs deficiency, the recycle defect. This is the kind of situation that shouldn't happen; if we've done all the science and we know how to treat it, we should somehow figure out the system to get them translated and make the system work for these kind of ultra-rare disorders.

Now, my own experience helps build some of the issues, I think, that are important, for laronidase for MPS I, in which the lack experience of biochem genetics [SP], both at companies as well as at FDA, made it difficult to understand how to manage a disease like this that was so rare. There wasn't enough regulatory science, in fact -- for around the surrogate endpoints or how you decide is this is going to work or not, how do you interpret the data, what do you make of it? We couldn't solve the questions that were asked; the questions needed to be answered, and without those, we're not able to use surrogate endpoints, which I think dramatically changed what was going to happen in that program. We ended up with further issues related to small clinical study designs and the

right statistical methods, and being pushed into using a new method that's commonly used for an endpoint when in fact, for a small study, it should've probably been another method. This is the integral tiny bits and pieces of regulation which are very difficult and which we need better guidance on so that people will make the right decisions and not end up making mistakes in the process of drug development.

Eventually, all this came up to an advisory committee vote, and the product was voted efficacious and we did get approved, and then a three-year delay occurred. But the more difficult problem is that the costs went up dramatically, probably three to four fold, and then in the same time, some of the products got knocked off our development path at BioMarin at that time. And those products still have no approved products at this point in time and that's been 10 years. So, there was a very significant impact when the costs goes up. And this is not a blame the FDA or anything; this is a situation that occurs and I think what we need to do is figure out among all of us scientists, FDA, and the public, what do we want for these kinds of endpoints? How do we want this development to occur? And we think that development of guidances and specialization FDA would help that.

In terms of the specialized review organization, the idea here is that there are people at FDA that are very experienced and knowledgeable in the rare disease area, and some of those should be allowed to be focused on rare disease type drugs. Now, that doesn't mean all rare disease; I mean, certain ones are not well covered. Some are very well-covered in their divisions where they are where certain ones which, I think, are not as well covered. I don't want to go into the scope issue right now, but by putting a group together, allowing them to work together as a team, and can stay together, the hope would be they gain additional expertise, leverage experience, and by bolstering that group with appropriate expertise that we'd end up with a group that gets better and better and more knowledgeable about very difficult complicated diseases. And we think one other part of this is that the work load on a group like this needs to be reduced because the applications are very complicated and there's a lot of unknowns, and whenever you're dealing with ambiguity, it takes more work, more effort, not less effort. And so that has to be accommodated, and I think we can't have people taking vacation in order to catch up with work. It's a reasonable solution to the work load issue; they have to figure that out. And the time they have to have is to be able to apply themselves to some academic links, to NIH, to also allow them to keep up with the latest of what's going on.

That improved academic structure, we think, is an important thing, that they really need to be able to connect in with meetings, and to have commissioners fellows that work with them, that are doing the hard, nitty-gritty work of understanding what's going on with this latest technology area and how do I relate that to drug development? The important thing is that it allows FDA to be proactive in dealing with small biotechs that are struggling trying to get somewhere, and I think the drug reviewers themselves must know the regulatory science issues. They can't rely on another group at FDA to tell them what they are; they really need to be able to understand them themselves because they have to sign on the dotted line, they are responsible, and they need to know them in order to be comfortable in making what are very difficult decisions because drug regulatory issues are complicated and always ambiguous and difficult at times. So, we understand how challenging it can be, but they need enough time and sufficient staff to make this work.

Go on to the next one; we'll skip this one.

So, let's talk about accelerated approval, the second goal. Accelerated approval regulations, I think, are a critical area for improvement, and the challenge is the law says they need to be reasonably likely to predict clinical benefit; that's what they say. The question is how do you interpret that? What do they really mean? And I think in the examples I have seen, the difficulty has been that there is almost never enough clinical data to help you prove the case is reasonably likely to predict clinical benefit. And therefore, you ended up, especially with some of these rare diseases, being unable to access this pathway.

Now, the difficulty with surrogates is that on the one hand, the FDA is getting critiqued for approving the things for type 2 diabetes, let's say, on a surrogate, and people are mixing up surrogate issues from [unintelligible] complexities with surrogates in rare disorders where there's a very unique, difficult situation for which it's not possible to do a survival study and where it's not possible to do the kind of work that you should be doing for [unintelligible] and type 2 diabetes.

So, because the surrogate endpoint story, and there's been a lot of attacks regarding using them in the large market, I think it's kind of caught up the whole rare disease area as well in that whole discussion, that debate. Now, I really think that they should be separated, and that in the rare disease situation there should be a different take and look at how you look at accelerated approval. And it should be separate and there shouldn't be any risk of a slippery slope between what you do in rare diseases with what you do for large market [unintelligible] where you need stronger evidence of proof and particularly safety.

By improving the uncertainty that exists today around the surrogate, you will turn on the investment of companies into this area, because if they knew that there were these certain things that they need this bit of data, they should have, they should do the work on, if they have this set of data that this is going to give them an acceptable surrogate, this allows them to start investment and begin doing drug development for some of these other rare disorders. Without that certainty, when they drop a net present value calculation, how much money they have to invest over time, and they're using a clinical endpoint and length of the studies and the time, they're going to come up with a number that's just too big and would never make any sense to do the investment, especially with the risk of failing. And that is what companies do. I was within a company; that is what we ended up doing.

I'm working now with my intern to write a paper which I'll show you. For a dozen drugs that clearly would work if translated to humans, that by looking at how if you apply a surrogate endpoint, you would dramatically reduce cost so that, for example, with a billion invested in drug development, you would get 40 drugs approved versus 10 or 12 if you used a clinical endpoint. We have to understand how those factors, how the predictability affects investment, and that's how we can help accelerate pulling in money from elsewhere that's working on way too many drugs that we don't need and get them working on new drugs for things that aren't treated.

We think that can be done by creating good criteria. So, one of the things I like to bring up is that the accelerated approval pathway has been difficult to use and that there's only been one genetic disease approved by this pathway; it's worked well for HIV and cancer. And I know accelerated approval recently had some critiques; the truth is the pathway has really been extremely important to HIV and cancer. And there have been some genetic disorders, because it was brought up by Dr. Goodman recently, for example, their PKU drug, sapropterin for PKU was approved on a biochemical endpoint, but -- it was given a full approval, but that is an unusual example -- or that exception proves the example of the case, which is in that situation, we had so much drug development data, -- or treatment data, excuse me, from another treatment that we could prove that the market mattered, but we rarely have a situation where we have 20 other controlled studies to tap into and to say, "Look, here's how it relates." That case just doesn't exist very often. And that's why it's difficult to use the accelerated approval pathway.

Now, what we've been trying to propose -- you need to go forward again.

All right. So, if you look at what's happened in HIV, there were 29 drugs approved in a period of 16 years with six different mechanisms of action -- six different -- including ones no one even conceived of at the beginning, and that's because a bunch of little start-ups with a little bit of money were able to get a little data and blow out all the ideas people had about how the treatment should occur and change the whole field, but that doesn't happen if they can't go to a VC and say, "Look, if I can do a 10 patient study and show I can reduce this marker, you know, we'll have something that's moveable," and that's how they get the money to make this happen, and that's how you take a disease from a death sentence to a managed disease.

I also point out to you that there were four combination products approved. And how many disease areas have combination products approved in that same time frame? Very difficult to do without accelerated approval, without the marker endpoints, to do combinations, to figure out how to do them well. This is why I think it would actually drive far better drug development than we can with just clinically-driven studies.

We think there's some simple things we could do in qualification criteria for surrogates, and I'm suggesting a few here that would help give us the scientific confidence that this would make sense, that the disease is understood, the drug is understood, and why the marker we're using makes some sense, but you shouldn't have to be able to have prior clinical data, because that just never happens. And that's where we ended up getting hung up with MPS I, and I think it's just we need to be able to figure out how to use the other parts of the science to make the judgment in a rare disease for which there might only be a few hundred people in the United States.

The last area I want to talk about is clinical data in heterogeneous patients, and it's extremely difficult, and maybe too arcane a topic, but we don't think that the current methods are often optimal, and the traditional approaches often are not very sensitive and are designed for larger patient studies where you get over the noise by simply having more patients. That doesn't work well, and I think there are many times with drugs that are for rare diseases where you'd list the treatment effect because the patients are so

heterogeneous and it's almost impossible to get enough patients of a particular narrow slice and condition.

And I think we need some better FDA guidance on what you could use for designs and analyzes. And in order to help inform on this we -- some of the Scientific Advisory Committee -- we're taking data from approved orphan drugs that we can get, and we're running analyses on them, which will look at different approaches, statistical analysis of a drug we know is successful, and then we'll model it using the treated and placebo groups to help show whether the method was more sensitive and also retained specificity; that is, we don't methods that generate false positives, drugs that don't work coming up positive, but we think by doing this analysis effort will help guide on what are the things that you can do in analysis of a small study or in design of it that will give you greater sensitivity and get the right answer, and that is showing efficacy and that it really does exist.

So, these are our three goals: getting the rights staff in place and help them give the staff that are here enough support and time to be able to do their jobs; and we think improved accessibility and predictability for getting into the accelerated approval pathway would be quite important; and finally, study designs and statistical analyzes. I think these three things would have an important impact in what we want. And we think what's going to happen if we get these things, more new drugs for rare diseases, I think there's no question we can get companies to invest to make that happen; we think we would get much more -- many more patients treated, particularly for diseases for currently -- might not ever get a disease treated developed. There are certain diseases that are just too difficult from a neurology basis, or bone, or whatever it is, that the [unintelligible] just won't go through because -- without these improvements.

And finally, we think, you know, on the timing, the economy is poor; I think these are -- there is a lot of high-paying jobs that come out of these programs, and I think it's a fact of understanding that this is an area where we can have a positive impact in doing good science, taking good science into great medicines. And the reason why we hope that this commission in doing its duties will help find this tractable approachable solutions, and we certainly hope that you get additional funding for drug review, and as well as help us find the way forward in getting drug development for rare patient.

Thank you.

Timothy Cote:

Thank you, Dr. Kakkis.

[applause]

Do we have any clarifying questions from the panel?

Emil Kakkis:

Thank you.

Timothy Cote:

Again, thank you.

Paras Patel:

Next we have Austin Noll, please.

Ninth Session

National MPS Society

Austin Noll:

Good afternoon. My name is Austin Noll. I am a member of the MPS Society's Board of Directors. I'm going to spend the next 10 minutes or so today talking to you about the importance of appropriate study design and the use of surrogate end points for the development of treatments for mucopolidosis and the family of mucopolysaccharide diseases. I would also like to take just a second to thank you for allowing us and for all these people here to be able to present to you today. Good, I've got it to work. You are going to see in my presentation pictures of kids throughout. And what I hope happens is I hope this underscores for you the importance of what you are doing here today. They are counting on you to make the right decisions. Now MPS and ML are genetic diseases that affect various areas of the body depending upon which specific type that you have.

There are seven conditions in all, and on the aggregate they affect one in 25,000 people. The commonality is they are all caused by an enzyme deficiency that results in the buildup of compounds in the cells. So this leads to cell death, system failure, and then eventual patient death. The most affected people die in their second decade of life. There are outliers; some die very early, some die very late, but again, typically in the second decade of life. And luckily there have been treatments developed for a few of these conditions. But it is important to note that even those conditions that are treated, when you have involvement in the brain and when you have involvement in the bone, those are not impacted. So those patients still suffer the effects in the brain and in the bone. The other four types have no treatments and there is minimal investment in the pipeline right now due to many of the reasons, frankly, that we have heard over the last hour and some of the reasons that Dayton just spoke about. Now, as I just stated, treatment exists for three of these conditions, MPS I, II and VI. But again these treatments do not treat the brain or bones; there are many conditions though that are not treated. So Sanfilippo, Morquio, Sly disease -- Dr. Kakkis walked you through that scenario about 40 minutes ago -- and then ML II and ML III.

As we've stated here numerous times, treatment for the brain and bone are hard to develop and they are hard to study in a way that meets the current FDA requirements. It's not to say that the current FDA requirements are bad, but they just don't work for these conditions. It's very difficult to measure clinical outcomes in the brain and in the bone. Clinical outcomes may take years to manifest, and the inherent heterogeneity of these patients really also adds to the clinical challenge. Because of these inherent challenges, these conditions have been less attractive to industry. And again, as Dayton said, you need to provide incentives for people to invest in developing these treatments. Industry is concerned with the uncertainty of the process and with the inherent risk and timelines involved with studies that require clinical outcomes measures and also the uncertainty of where that end point is going to be. It's critical that the FDA address and amend the clinical study process to make these conditions more attractive for investment.

Without this, frankly, it is very unlikely that we will see significant investment in treatments such as the ones that we have just discussed. Measurement of clinical improvement is difficult in brain and bone. It's also very difficult to reverse damage in those tissues, but it is not impossible. And I would also say that simply stopping the progression may be enough. In the brain with neuroplasticity, if you can simply halt the process maybe the body can compensate.

So the challenge is very difficult, but what do we do? Do we do nothing? Do we let these kids go? No, we need -- excuse me. We need access to designs that work for our patient population. We need sample sizes that reflect the rarity of these conditions. We need to do away with double blinded and randomized studies. We need to use surrogate end points when you can. Not every situation is going to allow a surrogate end point, but when you have the ability, please use it.

Simply put, the current paradigm doesn't work for rare disease. The current requirements are too difficult. They are too risky and too expensive to warrant significant investment for therapies. And our kids are dying. That's a fact. I see it every week as a board member. I know when every member of our society dies, two this week. With improved design we believe that the inherent development risks will be reduced, attract investment in potential therapies. Yeah, I am sorry, I know many of these kids whose pictures you are seeing, so it's impactful for me. We are requesting -- we are requesting specialization in drug review. We really support the efforts of the Kakkis EveryLife Foundation. What we need is a dedicated group of individuals to review treatments for genetic diseases such as MPS and ML. This group should consist of people trained in the intricacies of genetics and pediatrics. These are difficult subspecialties. You've got tremendously talented people here, but to be able to bring a lot of folks to bear, to look at some of these conditions is tough. You need a specialized group. We also request that surrogate end points, again, be allowed for studies where clinical end points are simply not feasible. And furthermore we request that study designs be revamped to limit the enrollment numbers to levels that are commensurate to the size of the patient populations that we are dealing with. These studies should be open label and not blinded. The kids deserve a chance, a chance to live. Thanks.

Timothy Coté:

Thank you, sir. Do we have any questions from the panel?

Austin Noll:

Any questions? Thank you.

Paras Patel:

Next we have Sharon Terry, please.

Tenth Session

Genetic Alliance

Sharon Terry:

Thanks very much for this opportunity to come here before you. I come on behalf of Genetic Alliance, which I think most of you know is a coalition, a network of about

10,000 organizations; 1,200 of those are disease specific and the rest are universities, industry, hospital, professional societies, et cetera. My comments are those of Genetic Alliance. In addition to what you see here and not on the slides, we also did a survey with your questions, and about a 100 organizations answered, and so I will be filling those in as we go; I will give you the complete results from that survey through e-mail.

Essentially we believe that -- and I -- by the way, I addressed just your questions. And I have lots to say about a lot of other things, but I will refrain today so that we can hear from everybody. Addressing the needs of rare disease patients, we believe that a refined guidance on specialty FDA product reviewer staff is needed, focusing on the challenges of small cohorts which we have heard a lot about today, marginal therapeutic effects, alternative end points, conditional approvals, routine accelerated reviews, and a longitudinal registry with post-approval follow up. We also believe that there should be the creation of a special orphan products review process within CDER. The survey that we took was about 25 percent disease advocacy organizations; the other 75 percent were industry, professional societies, et cetera. 88 percent said that currently FDA does not adequately address the review process at this time.

And the HUD/HDE population size, we have found that there is little evidence as to what effect the 4,000 person-per-year ceiling has on the approval mechanism. So, I stood here, I think it was two weeks ago, at the FDA NIH Regulatory Science Leadership Council testifying then, and I think what we talked about there is certainly relevant in the sense that we need evidence and data to understand what these processes actually allow. I think we should allow the secretary of HHS the purview to selectively raise the ceiling for specific conditions as appropriate to account for the unique needs of patients with rare diseases, and that population size should be considered in light of extreme need and on the inherent difficulty in drug development, handicapped by diminished statistical power, and that better defining what population subgroups are contained in the 4,000 person ceiling is also critical.

In addition, in terms of expense, that approval pathway of course is superior to PMA and 510(k) submissions, and that we should capitalize upon the data available; create a mechanism for post-market surveillance in order to track data on effectiveness of use and alternative off-use labels, label use; and post-market surveillance enabling FDA and other stakeholders to evaluate the value of certain devices.

The survey showed about a 50-50 split with a lot of people not really understanding the HUD and HDE pathway, so I don't think there was anything statistically significant there. In terms of defining probable benefit, I think we may be moving to the current evidentiary standards so as not to make the pathway rise to the level of PMAs and 510(k)s by providing guidance as to what types and quantum of evidence constitutes probable benefit; and then modeling some of this after the Secretary's Advisory Committee on Hereditary Disorders in Newborns and Children, which accounts for information provided by rare disease experts and grey literature. They developed a system whereby they can assess what diseases should be added to a [unintelligible] panel through a fairly robust process but one that certainly isn't as rigorous as you would have for more common conditions. And for this one, 91 percent of the surveyed said yes, that this could be defined better.

Communication with FDA, I think the “Build an Orphan” workshops, which the Genetic Alliance is a co-sponsor of, a very good first step, and we have heard very good in-the-field kind of reports back from those. I think engaging the rare disease community even more, and by the rare disease community I mean that to be both advocacy organizations as well as industry and those dedicated to this field, that we should have more workshops and work groups so that we are working together more often; more advisory committees and more representation from the disease communities and the industry folks who are a part of this community, and more special conferences that would look specifically at these issues.

The survey said that often the FDA’s engagement is too Washington, D.C.-centric, inside the beltway. I know that is often the perspective overall of people who live outside the beltway. I think probably using social technology and networking kinds of capabilities more robustly would help to alleviate that. And then I think just one of the comments that I found very well balanced was important, and basically this person said it was not uncommon for the public to demand less restrictive regulatory processes because we are concerned very much about those of us who have either children or ourselves with devastating diseases. What essentially, though, when you learn about adverse events and you learn about the risk in rapid approvals without a high regulatory bar, then we are disappointed as well. So there needs to be a lot of vigilance about what process we create; it needs to be flexible and iterative. We need to revisit it so that we gather the evidence we need to make good decisions. Thank you.

Timothy Coté:

Thank you, Ms. Terry.

Paras Patel:

Thank you. Next, we have Mike -- Mark Weinberg, please.

Eleventh Session

Lundbeck Inc.

Mark Weinberg:

Good afternoon. Thank you for the opportunity to speak today.

I’m the vice president of medical affairs at Lundbeck, Inc. Lundbeck, Inc. is a company that was formed in March of 2009 following the acquisition of Ovation Pharmaceuticals by Lundbeck from Denmark. It’s a company that is 70 percent owned by the Lundbeck Foundation and the mission is to improve the lives of patients suffering from complex CNS disorders and rare diseases for which few, if any, effective treatments are available. We have about 6,000 employees worldwide and 300 in the U.S. and I think are particularly pleased to be here today given that we have six rare disease therapies on the market, and that includes the first drug approved under the orphan disease act in 1983, Panhematin, as well as three drugs that have been approved within the past three years and one drug that is in late stage development that will be filed in the next several months.

What I'd like to talk briefly about is just a couple ideas on enhancements to the Orphan Drug Act, talk a little bit about the themes that have actually already been raised today about orphan drug development standards, the impact that REMS can have within an orphan disease, and the approval process and impact of conflict of interest rules, and really thinking about the fact that there are often many more similarities between orphan diseases in diffuse therapeutic areas than there are between non-orphan and orphan diseases within a therapeutic area.

First a few statistics, and some of these have been mentioned already today, but I think do bear repeating. I think that we are all very proud of the Orphan Drug Act. It was really visionary when it was brought forward in 1983 and the U.S. was at the forefront. Many other countries and regions of the world followed that type of legislation, and it really began to build a pipeline of rare disease drugs. I think without the incentives put in place that many lifesaving and life altering therapies would not be available today.

Prior to establishment of the ODA, there were only 10 approved orphan drugs; as of May of this year, 357 approved drug and biologic orphan products, a pipeline of more than 2,000 products with orphan designations. These designations are increasing. And as per actually an FDA presentation to NORD recently, about 25 percent of compounds were estimated to ultimately go on to receive marketing approvals, but I think the reason that we're here today is there's still great opportunity. With six to seven rare diseases affecting 30 million Americans, or 1 in 10, and only 200 of these diseases with a therapy approved to treat the condition, there's a lot that we can do.

The first challenge to talk about is how do we attract more companies to orphan drug development so that more therapeutic solutions are available to those in need? And I think it's pretty clear based on the comments that we have heard today that the incentives need to be expanded, that there's an opportunity for market exclusivity expansion, and I'll also touch on the criteria for orphan populations, as well.

If we look at market exclusivity, so, as we know, orphan drugs are often the only therapy for a given rare disease and should have, we believe, greater exclusivity than non-orphan new drug molecular entities. Given that the seven years of orphan drug exclusivity runs concurrent with the five years of Hatch Waxman, it's essentially a two-year benefit for orphan drugs. We strongly believe that that should be expanded to 10 or 12 years, as several folks have commented today. And really, this brings things in line with the 12 years recently awarded for follow on biologics and the 10 to 12 years available in the European Union. And I think some careful consideration of the model that's used in Europe where drugs are awarded a period of 10 year exclusivity with an evaluation that happens at the midpoint to determine if that exclusivity should remain. And then of course, they can get an additional two years for pediatric development.

The other thing that I think there's a little bit of consideration is what is the threshold for an orphan disease? And it is interesting that in 1983, that threshold was set based on a population of 200,000 when the population in the U.S. was 200 million, so .1 percent. Now, our population has grown significantly, but the orphan threshold has not. To recognize many of the diseases that we're talking about today are much, much lower than

that 200,000, but I think as the population in the U.S. continues to grow, we face a situation where drugs could be developed as orphan drugs and that disease could no longer be an orphan disease, sort of changing what the development focus might be.

The next point I'd like to make is just to talk a little bit about the complexities of development, many of which have been raised today, and then perhaps make some recommendations for how we could align what's done across orphan diseases. As we know, these are rare diseases which tend to be very difficult to study in clinical trials. And that's not just because the populations are small. It's because often, due to that, there's a natural history that's not well understood. There are endpoints for clinical trials that have not been well validated. We obviously need reliable outcome measures, tools, instruments, and biomarkers, and these things are, I think, more consistent, as I mentioned, across orphan diseases than within therapeutic areas.

There's clearly a longer timeline required for development of orphan drugs, and that's due to the small populations and the enrollment and often complicated by the fact that for adequate safety exposures, we need to go outside of the U.S. And four of these diseases in particular, I think the standard of care can really vary across the world. And clearly, this creates clinical availability, statistical variability, regulatory issues that really need to be thought about and that often delay programs.

What we see as the specific need is FDA focus on development of drugs for small populations. And I think it's commendable that the FDA has shown willingness to be flexible in the review of orphan drugs, but this really is not consistent or evenly applied. There's no overall statutory language to officially recognize these differences. And we would recommend a separate entity within FDA at the Office of Commissioner level with authority to case manage orphan drug applications to put the focus on the fact that these are orphan diseases and that we are pulling expertise from across the agency to really have a single point of contact to bring that in with responsibility for understanding how to meet these FDA obligations, but really to help drive collaboration across the FDA to harness what's learned within each therapeutic area with respect to dealing with orphan diseases.

Two other points that I think bear mentioning. The first is REMS. And we within the past few years have seen quite an expansion of the use of REMS to ensure patient to ensure patient safety. And one point that we would like to bring up is just the issue that this can have in a small orphan population and the potential for REMS to limit access due to specialists who are available, due to requirements for follow up, and due to logistics. And I think we need to recognize that some of these challenges are different within orphan diseases.

I actually bring up this example specifically; we have a product recently approved, Sabril, that requires some specific vision monitoring and need for neuro-ophthalmologists. And without an ability to get evaluations by neuro-ophthalmologists, patients can be forced to have to go off of the drug. And in the U.S., there are not a great number. In small cities, Savannah -- medium sized city, Savannah, Georgia, we've actually had difficulty where patients have to travel extensively, and within an orphan disease, that can severely limit the ability for the patient to get the therapy.

The other issue about REMS is they add considerable expense: additional phase IV four clinical requirements, patient registries, restrictive distribution, reminder system, enforced monitoring, collection and evaluation of reporting requirements. Across a large disease, this cost is not nearly as significant to the patient, but within a small disease, these same costs are amortized over a much smaller population. I think it's something to recognize.

There are, as I mentioned, more similarity between orphan therapies, and really, we believe that having instead of having therapeutic experts working on large populations defining how REMS might work within orphan diseases, we need orphan disease experts to assess the impact of the REMS requirements.

The final point to make is one of conflict of interest and insuring timely expert review of orphan NDAs. I think we have been very focused today in talking about the limited number of patients within these diseases, but we also need to recognize the limited number of experts. Clearly, you need experts that can develop drugs and that can also evaluate drugs. With a limited number of experts to participate in clinical studies, you often lead to having a very small group that can then evaluate. And recently, forming an advisory committee for one product had to be delayed five months in order to impanel an appropriate group for the advisory committee. We believe there should be statutory language to officially recognize the difference in expertise available between large and small populations to permit routine waivers of conflict of interest requirements for orphan drugs.

So, in closing, I would just reiterate the two main points that we really believe can increase and improve orphan drug development. The first is expansion of exclusivity and creating the incentives for companies, and we believe that should be expanded to 10 or 12 years. The second is recognizing the similarities between orphan diseases across therapeutic areas, and the fact that in some cases these may actually trump the similarities between non-orphan and orphan diseases within a therapeutic area. We believe that the creation of a commissioner-level office that draws expertise from within the FDA and leverages this orphan experience will enable the FDA, industry, academia, and patient groups best collaborate on effective and rapid drug development in orphan conditions.

Thank you.

Timothy Cote:

Thank you, Dr. Weinberg. Thank you for your contribution.

Paras Patel:

Thank you. Next, we have Chris Hempel, please.

Twelfth Session

Addison and Cassidy

Chris Hempel:

Dr. Cote and Dr. Paras and the rest of the panel, thank you so much for the opportunity to speak today. And the title of my presentation is "One Mom's Journey into the Valley of Death". I'd like you all to take a look at that picture up there. It's a very long road. That's a road that I'm on right now and the road that I really don't want to be on, but unfortunately, I really have no choice.

Let me see here. The red button makes it go? Okay.

Let me tell you a little bit about myself. My name is Chris Hempel and I'm from Reno, Nevada, and in 2004, I was blessed with identical twins, Addie [spelled phonetically] and Cassie [spelled phonetically], who are now six. Before becoming a stay at home mom, I had a career for close to 20 years in high tech public relations working with many Silicon Valley company startups and I'm a cofounder of a technology PR firm that's based in San Francisco.

And in 2005 my medical odyssey began with my twins, and that's when they were "diagnosed with a virus," which turned out not to be a virus; it turned out to be, after a two year odyssey, a Niemann Pick, Type C, which is a fatal condition involving cholesterol, where the cells don't process cholesterol. And the best way to describe this is essentially it's like a childhood Alzheimer's condition; kids kind of progress into a dementia.

So, over the past two and a half years, I have been working diligently to find treatments for my children, and I now consider myself a rare disease, I say "advocist": It's sort of the combination of advocate and activist put together. I don't really like that activist word; it has a very negative connotation, so I call myself an advocist.

Next. The -- the theme that I have found over the last few years in rare disease is that there's really not a lot of hope; it's just a common theme. There's millions of people that have these conditions and they get diagnosed and they expect to go to the doctor and find medications and they're told, you know, there really is nothing for you. So, this is just a common theme that's happening for millions of people.

And I'd like to point out in our disease, we have one experimental drug at the tune of \$160,000 a year for my twins, and I'd like to ask the FDA, you know, how can we fix this problem? You know, how can we be creating drugs today that are this expensive? I mean, there are many children in the United States; we have about 200 million cases in the United States, 500 worldwide. Many of these children can't even afford to have this drug, which is called miglustat, because the cost is so high. So, we have a drug, and yet people don't have the insurance and they can't afford it. So, I think we need to realistically say, you know, if we're building drugs, we need to build affordable drugs.

In our disease state, there's a lot of basic science when I first became involved, but really no therapy pipeline was built and literally no biomarkers in our disease. And one of the big problems I found is that the existing foundation's goals were not really aligned with my family's goals, which is I wanted to treat our children today. I don't want to wait five years from now. I don't want 10 years down the road. I want to find something that can help my kids today, and so that was when we started our effort.

Next. So we heard earlier from Jonathan Jacoby that we teamed up for created a group called SOAR NPC. We teamed up with five families to pool our resources; we created a virtual biotech, so to speak, which I think that many foundations are going to need to do if they're going to try to move drug development forward for their rare disease. because there just is no the pharmaceutical interest and the biotech interest is just not there for many, many of these rare diseases.

So, we decided we're going to have to create a virtual biotech. And so we hired a Ph.D. to help us sift through all the medical data and we're finding researchers that are willing to collaborate across their labs and not reinvent the wheel or not duplicate experiments. So, it's a very highly managed process and the parents have taken on this role, and we've created various goals, short term goals to look for FDA-approved drugs off-label that we could put into our kids today and to treat them today, and then the longer-term role, which is new drug development.

This slide says, "It's personal." It doesn't really it is personal, but it's a different point. Next.

"It's personal" has to do with this personalized medicine approach, and so what I quickly figured out is that the pace of research is just too slow to help our twins. And the only way to really attack this problem is really to try to go after a personalized medicine approach. And so essentially, you know, different drugs and therapies need to be based on sort of individual and genomic profiles, not these averages. And so we decided to sort of take this approach on making clinical decisions for our children based on their own personal genetic profile.

And we really inserted ourselves into the scientific process despite lots of resistance and lack of knowledge. I've I have absolutely no science background. I graduated from college not taking one science class and so it's a huge, you know, effort for parents to, you know, get involved in the scientific process but it's necessary, because it's very necessary to manage the process, especially with the researchers, but they're resistant.

Next. So, soon after we got our diagnosis, a promising sugar compound came to our attention called cyclodextrin. I know Dr. Cote and Dr. Paras are aware of this compound. It's used in the food industry. It's nontoxic and it has the ability to extract cholesterol from cells. And at the time, you know, we knew that there was limited animal data. It was promising, but I kept being told that cyclodextrin just was many years from ever going into children and that much more research needed to be done. And lo and behold, I started looking into it and realized that there really is a lot of data on this compound. I mean, there's a lot of safety data, this compound was already going into people from another drug, it was compounded with another drug, and so I thought, you know, this doesn't make sense. I mean, we really need to be working in parallel, but didn't really have a lot of support, I must say, from our community. And just in general, I think people it's just a very difficult process. So, we decided to enter sort of a this is when the journey into the valley of death really began. I'd like to say that I really believe next, sorry.

I'd like to say that I really believe that cyclodextrin is a perfect rare disease case study for both the FDA and the NIH. I think our personal experience really can show the challenges that we're facing in the rare disease system today. This compound, there's no real ability to patent this compound, and as a result, we have no pharma or real biotech interest other than just pro bono. I mean, I've begged Johnson & Johnson to get involved and, you know, slowly they are, but, you know, even if this was patentable, it's virtually impossible to just move this forward due to the costs, the risks, small patient population. And I mean, we have an orphan drug designation and it's like my phone isn't ringing off the hook from venture capitalists or I mean, there just really isn't any interest, and yet we have something so promising that is affecting the brain.

The next slide. So, our challenge is really, you know, how do we conduct an N of 2 human trial without pharma, biotech, or NIH support? And how do we move forward when some of our own researchers don't want to share data? This is a huge problem in science today is that many researchers are not aligned with trying to do drug development. They want to publish papers. They don't do their science for therapies for people, and so they're more interested in holding back data. So, here we are trying to move some preclinical work forward on humans, and yet the researchers want to hold back their data for publishing purposes. It's just a very sad state of affairs, I must say.

And our doctors, even in our own community, I think this is kind of a somewhat risky thing to do, and so when we have a few doctors, and I found a cancer doctor. The cancer doctor seemed to be a lot more aggressive and willing to take on these metabolic cases, and so our cancer doctor decided to help us and thought this was a safe compound. So, we embarked on writing a whole intravenous protocol from scratch with no FDA experience, and it's really a full time job and it requires a lot of personal funding. I mean, we're this is like hundreds of thousands of dollars. I mean, it's not a few dollars. Our insurance company supports us. Hopefully there's nobody from Blue Cross in the room, because I don't know why they're supporting us. This is, you know, technically, you know, somewhat experimental, but without insurance support, this entire thing that we're doing would be stalled, because we don't have the funding. It costs \$24,000 a month just to do the infusions in the hospital.

Fortunately, the insurance company is paying for the time in the hospital, the nurses, but interestingly, they weren't willing to pay for the cyclodextrin itself, and when what we later found out is that they believe that it was very expensive. They wanted us to pick up the cost for it. Well, you know, we thought it was kind of going to be like Cerezyme, very, very expensive, which it turned out that cyclodextrin is cheap. And so we're making these infusions bottles at about \$100 a bottle for our infusions at this point for our children. Our hope is to be able to provide this at some point to other children for that low, low price.

The next slide, I wanted to talk a bit about our FDA experience. The FDA did approve our intravenous INDs. I wanted to say that if I really listen to people that what people told me about the FDA, I would not be standing here today. Everyone just seems completely scared to death of the FDA. The FDA has been extremely helpful, you know, responsive, but I would like to tell you that the process is cumbersome. The rules and regulations when you're trying to run a sprint, not a marathon, is just overwhelming: the

amount of paperwork, the communication that needs to happen, the filings that need to be made. I mean, I have reams of binders and filings that we have needed to make for these INDs and, you know, my doctor is giving her time pro bono to help. It's not like you know, if she spent all her time just doing all the FDA work, she wouldn't have time to take care of patients. I mean, it's that mind boggling how much paperwork is involved. So, if there's a way to try to set up, you know, some groups that could help these smaller communities like ours, it would be very, very helpful.

I say here that we recently submitted new ideas because I put this side deck [spelled phonetically] in a few weeks ago. We're getting ready to submit a new IND in the next few weeks to do intrathecal delivery into the CNS so that will be another major hurdle that we'll need to cross with the FDA.

My next slide here is -- go ahead, pass the reality check. It's entitled "Stop the Spin," and that's just a term that's used in the PR industry and something that, you know, in my field, we do a lot of doing. And I think I'd just like to say that I really, you know I really do believe that the system is failing millions of people, particularly children. And it just seems like a lot of the data and things that are coming out, you know, comes out it's positive, but it's just not a reality check. I mean, we have in 25 years so few drugs for so many people and just something needs to change. Drugs are being created by pharma companies that people can't afford, as I mentioned, and the whole research system -- and this is not just the FDA's problem. I mean, this is a problem in the research system and the whole publish or perish and tenure-driven mentality.

And, you know, it's not focused on health and drug development. The people that are in research have no idea how to do drug development. I deal with these researchers all the time. They just have no clue. And, you know, there's a running joke that, you know, really it isn't the National Institutes of Health, it's the "National Institutes of Science", and we really need to have a National Institutes of Health and focused on drug development.

I believe all constituents, the FDA, NIH, pharma and researchers: I mean, we must admit that the system is broken and it's just on some level it's not working and that we need change today. We need more action and we need more sense of urgency.

The next slide. I wanted to talk a little bit more about the bench to bedside gaps. Moving compounds from the lab to humans is a major problem facing all rare diseases. Like I mentioned, the research labs have no idea how to do this, and it's really not in their charter to do it, and they're relying on pharma and biotech companies to take on this entire role, and the pharma and biotech aren't doing it. And because of the things people mentioned: there's lack of financial incentives and too much risk with too little upside.

And if you don't have pharma or biotech support, then reliance shifts then to the NIH to conduct the clinical trials. But the NIH is focused on research; they're not focused on like drug development and they don't even fully understand the process. I mean, we're asking, "What did the FDA say about that?" I mean, it's cozy. And the NIH, you know, I don't think they really know how to run these very small clinical trials, you know: two patients, four patients, eight patients. You know, they want to talk about large cohorts.

Well, what are you supposed to do in a disease that you've got 500 children worldwide? I mean, it's and you're filling up your pipeline with promising compounds. You've got to work with smaller groups. And until TRND, there really was a lack of government dollars, and I really, really want to emphasize just what an amazing pro REM TRND is and it really needs support and it really needs more funding because they're taking on a critical role of trying to find drugs for people.

The next slide, please, past solutions. So, you know, a lot of people want to talk about the Orphan Drug Act of 1983. I think, yes, that was a great act, but the incentives are outdated for today's pharma and biotech and venture capital needs and we need to do something. I was thinking that we could create something similar to the Priority Review Voucher system that was passed for infectious diseases. I was even thinking we could I call these things ODACs, Orphan Drug Act credits. Something that's modeled after clean energy credits and, you know, the idea is to let these blockbuster drugs fund the orphan drugs through patent extensions and priority reviews. You know, I don't know what the answer is, but we need something. The application that I have approved, it doesn't buy me it doesn't get me anything. I'm not getting any funding from that.

The next slide, please. And changing research incentives and this is something that maybe NIH can work FDA could work with NIH on. I don't think that public funding should go to researchers who are working in silos. NIH grants need to be refocused and we need legislation in there. And also, NIH, you know, could reward this collaborative and cross disease research efforts with ledger grants, with this focus on drug development and bringing drugs because, you know, you try to fill up your pipeline. I just don't think that the FDA is the problem here; the problem is in other areas. And I think we're [unintelligible] SOAR and other new innovative role disease models. And also, I was thinking possibly some sort of government CRO, like a government contract research organization to be coupled with TRND, because one of the issues I have is trying to get human studies done on my children and yet, you know, we don't have CLIA-certified labs. Research organizations, the researchers that can do the work aren't CLIA certified, and so it's very, very difficult to move preclinical and human work forward without a CRO, and this is a big, big problem.

The next slide. I was going to talk a bit about investing in education in genetic diseases. You know, two and a half years in trying to help the rare disease community, I honestly feel that the rare disease community does not really exist. I mean, there's 30 million people, and where are they? I mean, how many people in this room are from pharmaceutical companies? I mean, this place should be packed. If this was a public hearing on breast cancer, this place would be packed. Everybody would be in here; there would be presentations; people would be fighting for their time.

I really don't think that, you know, people even know that there's a rare disease community. There's too many groups that are thousands of groups that are fractured, they don't work together, you know. Even in the lysosomal storage disease groups, we could be working together to find ways to cross the blood-brain barrier. Nobody seems to work together. And I tell people, "Oh, you have a rare disease." They don't even they're like, "No, my kid has cystic fibrosis." I'm like, "Yeah, it's a rare disease". They don't even understand that.

So, I think there needs to be an education effort. I hope that Francis Collins, you know, he's often said that rare diseases, the ultra-rare diseases are going to solve the more common diseases. If we could get Francis Collins to help educate the public. And also, there's a serious lack of statistics, and I know, Dr. Cote, I've asked you for statistics, but for such a huge public health concern, I mean, we need a lot more statistics on this process. And I really believe that we need an urgent economic assessment. What are rare diseases costing U.S. taxpayers? We hear about how much Alzheimer's is going to cost the taxpayers. What are rare diseases going to cost? That way your groups and the FDA and other groups can get more funding because, you know, we're driving the agenda with this data.

And then genetics investment I believe is critical. Genetic testing before people have children because we spend a million dollars, you know, trying to get a diagnoses for MPC. It's happening across the board. It's killing our health care system with how much how long it takes to get diagnosis.

So, the bottom line here -- I'm sorry if I got over time -- I really believe without novel financial incentives, changes in research incentives and serious government intervention and commitment rare disease drug development is not going to change.

Thank you.

Timothy Cote:

Thank you, Ms. Hempel, your story is important and we're grateful to hear it.

Paras Patel:

Thank you. The next presentation requires some equipment change, so it will be a good time for a break. We will meet again at 3:10. Thank you.

Thirteenth Session

Autoimmunity Research Foundation

Paras Patel:

Okay. We can go ahead and get started. Everyone please have a seat. We have Trevor Marshall next.

Male Speaker:

Welcome Dr. Marshall.

Trevor Marshall:

Thank you, Mr. Chairman. It's great to be here at this lovely meeting facility here at FDA White Oak in this wonderful building.

Well, the Autoimmunity Research Incorporated, Autoimmunity Research Foundation is a California 501(c)(3) nonprofit and we have applied for eight orphan product designations since 2005. Two have been granted -- for minocycline and clindamycin in sarcoidosis --

and six are still awaiting designation -- in sarcoidosis, the progressive phases of multiple sclerosis, amyotrophic lateral sclerosis, and PTLDS. These rare diseases have been our focus because they not only kill, but because they cause untold suffering amongst the families and caregivers. This presentation we will discuss our experience with the way FDA evaluates scientific data in the rare diseases. And since I'm an academic, I trust you'll excuse me if I don't go point one, point two, point three.

There we go. Not quite sure what's happened to my mouse. There we go. Okay.

The steps for approval in rare diseases, as I understand it at least, are basically that an orphan designation is sought, then the product goes to IND, and finally the product goes to NDA. Orphan designation is determined determines that the product shows promise, IND primarily focuses on the safety, and the NDA is where you demonstrate efficacy. The financial incentives are provided once you've got your orphan designation when the product actually supplies shows promise.

And if you just excuse me a minute, I'll have to solve this technical problem. Sorry about that.
Okay.

So, a colleague and I attended the first Orphan Drug Workshop in February which was extremely helpful. We got very good mentoring on what was required of the process. We figured we were going to be able to improve our hit rate a little bit from the two in eight that or two in six as it was at that time. And after that workshop, we submitted two requests for designation: one in progressive phases of MS and one in ALS. So, at the Orphan Drug Workshop, we were counseled thus as to what the objective is. The chief task of the orphan status designation application is to convince FDA/OOPD of two things: that the proposed product is for a rare disease -- that is, fewer than 200,000 persons in the U.S. had that rare disease or condition -- and that there is a medical rationale for believing that the proposed drug has promise for treating the rare disease or condition; that is, clinical data, animal model data, or rarely in vitro data, but not exclusively theoretical considerations. This major content of an orphan status designation can often be gleaned from the medical literature alone.

So, I think that the main concerns in my mind come down to evaluating the promise of clinical data. This foundation has had six applications rejected on grounds very similar to this one: "For the purposes of orphan-drug designation, sponsors need to provide data from either human experience or that the drug has been tested in an animal model that is generally recognized as appropriate for a disease, and that the drug has demonstrated activity." This was in a letter from Dr. Timothy Coté just two weeks ago.

The problem is this. Can I have the next slide, please? The problem is that, you know, "we don't treat the lab, we treat the patient." This is a quote from Yehuda Shoenfeld, a fellow of the Royal College of Physicians, editor of a number of peer reviewed journals, and there's it's 10 years almost to the day since the first human genome was completed. We now have also completed several animal genomes and several thousand pathogenic genomes.

Now, understanding of the way that living things work has just blossomed exponentially in the last five years. And what we're finding is that the models that we used in the 20th century -- the animal models, the in vitro cell line models -- are just failing when you start to examine the individual genes involved in the disease process. There's a huge disconnect between what the clinical professional, certainly clinical research profession, and what FDA reviewers seem to regard as promise.

Next slide, please. You see, men are not tall mice without tails. Well, it's important. In fact, my colleagues and I have just written a chapter for an upcoming medical textbook on metagenomics which explains in detail the many reasons why men are not tall mice without tails. We used the latest genomic and molecular technologies to explain precisely why animal models have consistently failed to provide solutions for patients suffering from chronic diseases. Every animal model has a different immune system from what we have. A mouse has a particularly different immune system from what we have.

Next slide, please. And our drug is a human VDR agonist. It only works in human beings. How do we know that? Well, we can take the gene of the receptor targets and translate that gene into proteins, locate the proteins in space with modern technology, and we can actually show exactly how the drug affects the receptor it's targeted. There's nothing magic about this. This is used by all the major clinical all the major pharmaceutical research companies.

Next slide, please. And our drug doesn't work in a mouse; it only works in Homo sapiens. Here's a video which is an advanced technique called molecular dynamics. And here you can see the protein is actually moving, because all proteins in our body are moving at all times as the moving at all times as the atoms try and find their minimum energy position.

Now, in the rat, we have a very similar situation based on the situation with the receptor and here is our drug sitting in the binding pocket. And this particular tetrazole [unintelligible] is what I'd like to draw your attention to. You can see that in the human and the rat, the tetrazole is binding to totally different amino acids. The rest of the molecule is roughly equivalent, but there are two hydrogen bonds missing in the rat because the actual amino acids in the receptor of the rat, which look, at first glance, to be the same as man, are not actually the same as man.

Can I have the next slide, please? Our recent applications for orphan designation offered 20 of our peer reviewed papers and conference presentations as literature. We even included a paper from a different research team showing that our drug doesn't even metabolize from the GI tracts of mice, quite apart from whether it affects the receptor correctly.

Next slide, please. Yet the FDA stated, "In a request for designation, the human experience data that was submitted are inadequate. The two case studies that were referenced in the application were anecdotal. In the absence of human experience data with defined endpoints, we would accept animal data with objective outcome measures." Let me read that again: "In the absence of human experience data with defined endpoints,

we would accept animal data with objective outcome measures. There is an accepted animal model of MS called Experimental Autoimmune Encephalomyelitis. No adequate preclinical data was submitted using the EAE model, or any other animal model of MS.

Next slide, please. We have a basic problem. Whereas we are focused on patient-important outcomes, FDA really would like to see mouse-important outcomes. They would really like to go to the phase where you can take an EAE mouse, such as these graphs show, you can inject it with a drug at day 10 -- day 10 here -- see something is happening here at day 14, and something is happening here at day 20, and say, "Okay, we look at these graphs; we can see there's a response. That's very good. We like it." What we're interested in is the smile on the face of the patient, the smile on the face of the caregiver. Much harder things to quantify, but nevertheless, they should be our goal as we try and improve the drug pipeline in these diseases.

Next slide, please. Here's one of the case histories that we had submitted. This is a case history which we submitted to the International Congress on Autoimmunity in 2008. It's a case history which was presented by Dr. Greg Blaney from Canada and it is for a progressive MS patient followed from 2006 right through to 2010, about four years. You can see there's quite a lot of blood work data we provided. And in particular, the NDSS, the disability scale, the NDSS scale, which is surely the most important endpoint to physicians who are treating MS patients, is here. And you can see it started at 8.5 and then anatomically dropped down to 7.0 over the three and a half years of therapy.

But let's look for endpoints in the actual descriptive text. The patient is a 56 year old female diagnosed relapsing-remitting 1995, progressed to NDSS 8.5 by September 2006 with paralysis in both legs and pelvis, obviously incontinence, refractory to treatment. Olmesartan -- which is the drug that we are trying to get through the IND, NDA pipeline -- olmesartan was commenced in March 2007. By June 2007, just three months later, the lower spasticity had moderated, and by March 2008, it had dropped to mild. By January 2010, the patient could walk 15 to 20 steps without assistance. Think of that. Think of what that means to the patient's smile, to get back some degree of independence where they could actually walk 15 to 20 steps without assistance. They could contract quadriceps and hamstrings against resistance, another endpoint. Depression was minimal, another endpoint. Spasticity minimal, and they no longer need to wear Depends. Isn't that an endpoint? That the patient doesn't have to wear Depends anymore? Another endpoint. Improvement remains continual and incremental.

Next slide, please. So, what did the FDA mean when they classed our data as anecdotal? That had come from a conference that had been through at least some level of peer review and suddenly had been seen by thousands of people who are at the Autoimmunity Congress.

But the NDA phases are run where you have to demonstrate efficacy, so how comprehensive a clinical study was OOPD expecting to demonstrate promise? We gave two comprehensive case studies. How many did they want? What did the FDA mean by "absence of defined endpoints"? I mean, what is an absence of defined endpoints? Why did the FDA suggest a mouse model when our application clearly described why a mouse model fails?

Well, I can't tell you the answer and I can't tell you the answer because there's no transparency in the process. We filed an application and three months later we got back we filed two applications, actually -- and three months later we got back two rejection letters which basically rejected everything that we had submitted.

There clearly needs to be some transparency or accountability in the orphan designation process. Why didn't somebody pick up the phone and say, look, I know you say that your drug doesn't work in a mouse but, you know, tell us more about this. Why can't you get the mouse data? But no, that wasn't the approach that they took.

Next slide, please. This word "theoretical considerations" -- how did FDA and OOPD reviewers decide when advanced science in peer-reviewed scientific papers and textbooks is to be considered theoretical and not literature? Because if you remember, the guidance said that don't use theoretical considerations, but sometimes you find the answer in the literature alone. Well, how do they determine it? Is it just based on the article is easy to read? Where does this fit? I can't tell you. There's neither transparency nor accountability in the reviews of orphan products that we have been involved with. We would submit that theoretical considerations cannot be precluded from any evaluation of promise. Submitted peer reviewed papers must be considered as promise and not as theoretical, whereas part of the drug discovery process involves theoretical considerations.

Next slide, please. Look, when I come up with a new idea or hypothesis, I have to go out and persuade people; I have to defend that hypothesis. Here's a keynote presentation I gave at the World Gene Congress in December 2008. There are some of the top geneticists in the world were there. There's a Noble Laureate that spoke immediately before me. If I had been talking rubbish, I would be cut to shreds. There's total accountability -- as far as I'm concerned, there's total accountability on the academic side of things. Why is there not that transparency and accountability? Those of you that want to read what I talked about, it was written up in "Personalized Medicine" and there's a citation for it.

Next slide, please. And just last month -- no, just this month, earlier this month -- last month [laughs] I'm sorry. Just last month at the International Congress of Autoimmunity in Riviera, once again, I was chairing a session there; you can see me giving a presentation. I'm the tiny little speck there on the right. This is a huge conference, 1,700 rheumatologists and researchers from all over the world. Scientific progress requires accountability and transparency.

Next slide, please. And here you can see that accountability and transparency in action. This is at the Asian Congress on Autoimmunity, and here I am up on the screen, because I'm asking a question of the speaker who had just given a keynote, and begging to differ with him on a few points. You can see it's a fully animated conversation because I have my hands moving. Thank you.

Next slide, please. So, here's the dichotomy. We have FDA/OOPD saying that our discoveries are theoretical -- at least, I assume that's what they're saying. They're

definitely saying they show no promise, but yet our peer reviewed publications continue to mount, the science is there, the pathogenesis is there, the cause is being established, invitations to chair conference sessions continue, and our members continue to recover their lives. Our members continue to recover. So, what happens when the patients decide we can't trust the FDA to look after us? Well, the result is chaos. Uncontrolled experimentation.

Next slide, please. You see, there's a risk-benefit ratio in rare diseases. These patients are facing imminent death and disability; their families are dysfunctional. It is terribly difficult to be a caregiver for somebody with one of these serious terminal rare diseases.

So, this is what happened back in 2007. Dr. Timothy Coté wrote to us in 2007 concerning our request for orphan drug status designation for a drug, Benicar -- which is a [unintelligible] olmesartan -- in the treatment of sarcoidosis. "Regarding the request for the orphan drug status designation for Benicar for the treatment of sarcoidosis, we have reviewed the entirety of your submission, including all written and electronic materials. We find that the website access you granted us did not include interpreted data supportive of granting orphan status designation. Neither did your written materials establish medical plausibility for your request. All five of our reviewers separately came to the same conclusion."

"All five of our reviewers separately came to the same conclusion," however, the papers that we had published and that successes being openly reported by patients on a variety of Internet sites showed enough promise to the sarcoidosis patients and to their physicians that hundreds, perhaps thousands, have commenced uncontrolled experimentation.

I did a Google search just a week or two ago for Benicar and sarcoidosis and there are 402,000 pages, web pages on the Internet talking about Benicar and sarcoidosis, something that OOPD decided in 2007 that there was no medical plausibility for it.

Next slide, please. The first page listed by Google is one of our own papers from 2003, and the second page that Google ranked as number two was this one from another nonprofit, the Foundation for Sarcoidosis Research: the Stop Sarcoidosis Support Community. The patients have gone well beyond whether the drug works, whether the drug has potential; they're more worried about getting insurance so that they can stay on the drug until they can recover. Not only is it beyond the stage of hypothesis, beyond the stage of plausibility, beyond the stage of promise, it's now out there in the wild. We have no control over it. We can't tell them that the doses they're using are wrong. We can't tell them that in two years' time, when their immune systems fully kick in, then they'll find immunostimulation is not such a big not such a great thing at all. We can't tell them; as sponsors, we've totally lost control of the situation. It's gone viral. FDA also has no control of the situation. This particular [unintelligible] is being prescribed off-label and people are flourishing with it.

Next slide, please. So, to summarize our experience, in my opinion, it's clear that FDA needs to define procedures to acquire the expertise to properly evaluate genomic and molecular science, what I think they currently call "theoretical considerations". The orphan designation progress the orphan designation process must develop both

transparency and accountability with sponsors and the public. The public are stakeholders, too. The public is now empowered by the information that they can get through their support networks and on the Internet and we're facing a totally different future from what we were looking at five and 10 years ago.

We would like to help FDA set clinical endpoints which are more relevant to actual patients and their families. I think that FDA has been looking for fairly easy to characterize endpoints, such as blood metabolites of mouse models, even if those bear little relevance to patient best outcomes. FDA needs to also weigh the risk-benefit ratio of the doubly rare diseases, especially progressive MS, sarcoidosis, and ALS. Our therapies, which offer comparably acceptable risks, [unintelligible] of drugs that are already on the market. Our therapies had been rejected without any regard to the imminent disability and death which were faced by the patients with those rare diseases, and as a result, it's got out of control.

Thank you very much, Mr. Chairman.

Timothy Cote:

Thank you, Dr. Marshall. Thank you so much for your comments. For the record, I do want to note that between 70 and 80 percent of our orphan status designation applications actually do result in the granting of orphan status designation, and I'm sorry that your experience was different. But thank you for your contribution.

Trevor Marshall:

Thank you.

Paras Patel:

Thank you. Next we have Art Kessler, please.

Fourteenth Session

Dystonia Medical Research Foundation

Art Kessler:

Thank you for inviting me here today. My name is Art Kessler, and I am president of the Dystonia Medical Research Foundation, or DMRF. The DMRF is a patient-based, nonprofit organization dedicated to serving all people with dystonia and their families. Since its inception, the DMRF has grown from a small family-based foundation into a dynamic membership-driven organization led by a board of directors and network of volunteers who are united in our goals of research, increasing dystonia awareness, and support for those living with this disorder.

Allow me to begin with a quick overview of dystonia. Dystonia is a neurological movement disorder that causes muscles to contract and spasm involuntarily. Dystonia is not usually fatal but it is a chronic disorder producing symptoms of varying degrees of frequency, intensity, disability, and pain. The DMRF is part of the collaborative effort known as the Dystonia Advocacy Network, or the DAN, which works to represent the individuals affected by dystonia. The DAN is comprised of the Benign Essential

Blepharospasm Research Foundation, the Dystonia Medical Research Foundation, the National Spasmodic Dysphonia Association, and the National Spasmodic Torticollis Association, and ST/Dystonia, Inc. Because dystonia hits so close to home for our directors and volunteers, the DMRF leadership and now our partners in the DAN, we are motivated by [unintelligible] drive to find a cure and an unwavering commitment to serving people affected by dystonia.

Until a cure is discovered our utmost priority remains the development of approved treatments for patients. A number of medications and therapies are currently available to help patients to manage the symptoms of dystonia, but we are finding what works for each individual is a process of trial and error. Treatment for dystonia remains highly individualized, and patients often try numerous therapeutic options to treat painful and debilitating symptoms. Two treatments, botulinum toxin and deep brain stimulation, or DBS, are considered particularly beneficial. Botulinum toxin injections and DBS carry the promise of the freedom to move and the freedom to control their own bodies for many dystonia patients. These treatments have allowed many dystonia-affected individuals to return to work and lead productive lives. The way it works, [unintelligible] a nerve blocker attaches to the nerves that connects to the muscles to prevent the release of a neurotransmitter that signals the muscles to contract excessively. By preventing the release of this neurotransmitter the neurotoxins reduce the intensity of dystonia symptoms, in many cases providing pain relief and the ability to move again.

I am sure many of you listen to the Diane Rehm on NPR and have heard at one time or another that she is out of the studio receiving her voice treatment. This treatment is for spasmodic dysphonia, a form of dystonia, and most likely consists of a series of botulinum toxin injections into her vocal cords. Before we go on, I'd like to show you two quick video clips. The first is a dystonia patient before botulinum toxin injections, and the second is after. These should help you better understand why maintaining and improving access to botulinum toxin injections is such a high priority for the dystonia community. The woman you are about to see has tongue dystonia. [unintelligible] play the video. That's the second one. Can you play the other video?

Can we turn the sound up? Okay, well, you can see that her tongue moves uncontrollably and obviously that's going to affect her speech. Okay, this is her after her injections, and you can see now that she has got control of her tongue. And if the sound was working, you'd see that she is speaking much more clearly. For this woman, the treatment is really life changing for her. She can now -- she is now able to venture out without people staring at her because of how her tongue moves, and she talk much more clearly.

[unintelligible] joined other patient organizations in urging Congress to establish an approval pathway for generic or follow-on biological products that maintain strict patient safety standards for new products. Botulinum toxin is a biologic and also highly dangerous substance. As FDA works to implement to promote the follow-on biologic approval pathway, authorized by the Patient Protection and Affordable Care Act, the DMRF and DAN members look forward to open communication channels in a transparent process as a stakeholder.

It is our hope that we will be able to provide clear cut input at every stage of the process and that FDA's goals and objectives will be well articulated to the patient community. We applaud FDA for your work on the follow-on biologics approval pathway thus far, and we look forward to working together and moving forward to insure that dystonia patients have access to additional safe and effective biologic products.

The second treatment that I like to discuss today is deep brain stimulation, or DBS. I can personally speak to how important this procedure can be for a dystonia-affected individual, because I have undergone it myself. I was diagnosed with early-onset generalized dystonia, dystonia that affects my entire body, when I was 12 years old, after four years of unexplained symptoms. My symptoms relentlessly advanced and in 2007 became too painful to walk to the park with my son. I had decided then to undergo DBS, and the results have been life changing. My wife and sons now have a husband and a father who, despite having dystonia, is physically able to be active and a part of their lives. In fact, this past May I walked around Capitol Hill for over six hours as part of the DAN's Dystonia Advocacy Day and while the [unintelligible] was tiring, it was also pain free.

It is said that a picture is worth a thousand words, so I would like to show you two more clips. The first is of a dystonia patient before DBS and the second is after. This is a young man who has generalized dystonia that affects most of his body. As you can see, he has trouble sitting, standing, and his gait is unsteady. You will see him walk in a second here. And this is typical of the effects from generalized dystonia. This is him after his surgery. As you can see, he is much more in control of his body. He is able to stand up straight. You will see him walk in a second here. His walk is more steady. And I am pleased to say that he is now enrolled in college and doing very well.

DBS targets the globus pallidus of the subthalamic nucleus of one or both sides of the brain with electrical stimulation to relieve the muscle contractions that characterize certain types of dystonia. The treatment uses a surgically implanted medical device similar to a cardiac pacemaker to deliver carefully controlled electrical stimulation to precisely targeted areas within the brain. The system itself is composed of three parts: a lead, which is four thin wires with four electrodes at the tip; an extension, which is four wires threaded under the skin from the head down to the neck and upper chest; and a neurostimulator, which consists of a battery and electronics and is implanted below the collarbone. A clinician can control the DBS pulse non-invasively with the programmer, which uses radio telemetry to check or change the nerve-stimulator settings. DBS was approved by the FDA as a humanitarian use device, or HUD, for the treatment of chronic, intractable, primary dystonia, including generalized and segmental dystonia, hemidystonia, and cervical dystonia in patients seven years and older under a 2003 humanitarian device exemption, or HDE. The FDA has made substantial progress with HDE process, and as a result many dystonia patients have increased access to DBS treatments.

I can tell you that dystonia patients have been denied coverage for DBS even after the procedure was recommended by a medical professional and have approached the DMRF for assistance with their insurer's appeals process. In these situations, out-of-pocket costs alone present a significant obstacle to receiving treatment. We appreciate that the

coverage denial by insurers commonly stems from DBS's designation as investigational. We recognize that FDA does not have authority over HUD coverage policies, but the frequent denials of coverage is a real barrier to patient access to these life-changing treatments, and it is one of the limitations of HDEs. We encourage the FDA and the industry to actively work to remove the investigational designation, thus removing the barrier to this life-changing treatment. In this regard, as a rare disease, the patient base for specific types of dystonia does not exist to conduct the clinical trials necessary to determine efficacy under the FDA's pre-market approval requirements.

The PMA approval guidelines for rare disease treatments set forth by the Center for Disease and Radiological Health do not appear to take this obstacle into consideration. In fact, the requirements and standards for rare disease seem to be the same as the requirements and standards for large patient populations. Perhaps CDRH could exercise discretion in its data requirements for PMA approval and could take into consideration the hurdles surrounding approval of treatments for rare disease conditions like dystonia.

Ultimately a separate process is needed that facilitates the approval of HUDs and appreciates the unique challenges of developing a product for a rare-disease population. The dystonia community greatly appreciates the FDA's progress thus far in making DBS more readily available through the HDE process, and we hope that the FDA will take proactive steps to see that the HUDs are more easily accessible to rare-disease patient communities beyond the HDE process. By working to facilitate the overall approval of HUDs and removing their investigational designation, we will be preparing for the future by recognizing that advancements in technology will increasingly lead to situations where innovative and existing devices can treat multiple patient populations, including rare disease communities. For example, DBS is currently also approved to treat Parkinson's disease and is currently being investigated as a treatment for a number of other conditions. Thank you for your time and for the work you do to ensure safe and effective medical treatments. I appreciate your consideration of the Dystonia Advocacy Network's recommendations.

Timothy Coté:
Thank you, sir.

Sheila Brown:
I am Sheila Brown with the -- I work with HDEs. I just wanted to clarify that we do not consider an approved HDE to be an investigational device.

Day 1 Meeting Close

Timothy Coté:
Okay, thank you so much. Okay, I think we have run through the docket today of today's planned speakers, so we will adjourn, and tomorrow -- I am sorry, yes, the slides --

Elizabeth McNeil:
We have had a number of questions about the presentation, the slides that have been presented here today. They will be posted to the docket, but it probably will be about a

week or so delay before you will actually see those. But then anyone will access them through the same docket that brought you here today.

Timothy Coté:

Tomorrow we have a few more planned speakers. Look forward to hearing from them, and then there will be an open mic session as well, which will follow immediately after the planned speakers. And then we will adjourn. Again, thank you all for coming. I know that it has been a long day and it has been a lot of listening, but there has been a lot to hear, and we look forward to hearing more tomorrow. Thank you again.

Day 2 Meeting Open

Timothy Cote:

Good morning. We're going to get started, so please feel free to take your seats and we'll get rolling.

Again, most of the introductions were given yesterday. This is the second day of a two-day -- well, probably one-and-a-half-day meeting on the topic of the FDA Review of Articles for the Treatment of Rare Diseases. My name is Timothy Coté. I'm the director of the Office of Orphan Products and I'm also the chairperson of the congressionally mandated Section 740 Committee, which is charged with reviewing the policies and procedures by which the agency reviews articles for rare diseases.

I'm joined at today's -- today again, as yesterday, with Dr. Elizabeth McNeil, who's also from the Office of Commissioner here. She serves as the executive secretary of that committee and will be formalizing the report for the commissioner -- the Commissioner's Report to Congress -- well, she'll be drafting it, and the commissioner will be actually the person responsible for it, moving it on to Congress -- and it will include many of the excellent comments that we heard yesterday from a wide variety of speakers. And so those of you who were here know how valuable that's been, and those of you who weren't can probably look at most of it that's being held up in the docket.

Today, we have an abbreviated day. We did most of our work yesterday. And again, the mechanism of this meeting is a Part 15 meeting, which is it's the official means by which the agency receives input from the public. So, most of our job at the agency here is to listen today. That's why we have very little in the way of formal contribution to this meeting; it's mostly active listening. You may hear occasional questions for clarification, but in the main, we're not here to answer questions or engage in dialogue but rather to listen, to think, and to hear what people have to say about those questions that we put forward in the Federal Register. Those questions are the same questions that the committee is trying to answer, and we can't really do it without your public input. So again, we need you. We're grateful for your coming, and we're looking forward to hearing more today.

So, with that, I will hand it over to Paras Patel. And [unintelligible] Patel?

Paras Patel:

Good morning. Welcome to White Oak Campus today. Today is June 30th, 2010. This meeting is being transcribed. All presentations, comments will be submitted to the open docket, Docket Number FDA-2010-N-2018. The docket is open for public comment until August 31st, 2010, and can be found at www.regulations.gov. The meeting today is also being Webcast.

And with that, we'll go ahead and start our first speaker. We have Susan Alpert, please.

Fifteenth SessionAdvanced Medical Technology Association

Susan Alpert:

Good morning. I'm very pleased to be able to speak to you this morning about issues related to the Regulation of Articles for the Treatment of Rare Diseases.

Small populations present unique challenges, both for the development as well as the regulation for regulated products, and it's timely that we're discussing it at this time while there's so much debate going on around health care. And this is a rather important area for many of us.

Just for full disclosure, I work at Medtronic, which is a medical device manufacturer. And by previous background, I am both a pediatrician and I had 13 years at FDA, so I have some perspective on both the development side as well as the regulatory side, and from a user perspective, the needs of small populations.

So, in the next few minutes what I'd like to do is talk through a little bit of background, talk about the challenges for developing products in this arena, and make some suggestions and proposals for things that FDA might consider in being able to advance the ability of products for these unique populations to move more quickly and more efficiently through the regulatory process.

I'm, as you know, speaking on behalf of AdvaMed, which is a trade association. AdvaMed represents manufacturers of medical devices, diagnostics, and health information systems, and we're the largest trade association, and we represent the majority of medical technologies that are affecting health care both in the United States, and about half of the medical technologies actually that are impacting patients around the world.

Medtronic as you know is a medical technology company. Our focus is on chronic disease, and we work in a wide variety of areas in chronic disease. We alleviate pain, restore health, and extend life with our therapies. And again, we're on the larger side. We are more than 40,000 people. We work in 120 countries, and, as I said, in a wide variety of chronic disease states, with various types of products -- not just PMA products, but many 510(k) products as well. We have some diagnostics, as well as many therapeutics, and some that are on the cutting edge of those therapies. So again, the breadth of products that really can, in fact, impact the populations we're talking about.

I think it's important to recognize that there is a difference in the extent of which the orphan product processes have been used in the pharmaceutical area versus the medical device area. And I'm going to talk, both now and in a little while, about some of the differences in the processes that are in place and the approaches that are in place. Again, briefly, for orphan drugs, there've been about 350 products approved through the orphan drug process, which I know you're familiar with.

On the device side in the process, you can see that although 232 HUD requests, Humanitarian Use Device requests, have been received, less than half of them have received the designation, and only about a third of those have actually moved forward to HDE, Humanitarian Device Exemption, approval. And then clearly the next step for those not familiar, HDEs -- and we'll talk a little bit about this in a moment -- have some limitations on them, and in order to move from an HDE approval, which has limitations, into full PMA is quite a process that we'll talk about. It's one of the areas that we want to discuss. And only three of those 50 have moved forward to full PMA approval. And that poses significant challenges, both for the industry as well as for the availability of these products for the patients in need.

I'm not going to read the questions. We paraphrased the questions that were asked, but we believe that there are really issues in all of these areas, both from the standards that are applied, the designation process, and how companies become aware of the appropriate ways to utilize HUD and HDE, the standards that are in place today for approving such products, and again, the communications that we believe are needed to improve the process, as well as to make the process much more visible.

On the device side, for those not familiar, device populations are quite a bit smaller than pharmaceutical populations, so our targets, even in the best of cases, are not all that large. So, the added issue of having a small population rare disease, or in the case of pediatrics where many of the diseases affect a very small proportion of children, those present very unique and difficult problems for developing the types of particularly clinical information that are necessary for receiving both either an HDE or a PMA, a full Premarket Approval for a medical device.

The small market size is a challenge for many companies. The medical device industry is very different in its composition. The vast majority of companies in the medical device arena are quite small; 65 percent of companies have fewer than 50 employees, so we're talking about a very entrepreneurial and small industry, an industry that is frequently supported by venture capital money and other types of investment rather than revenue streams from currently marketed products. So, we have a very small segment of the industry that are large companies that are sustained by current markets, and a wide swath of companies that don't have any products in the market or maybe have one that are supported in other ways. And so the small market size does have an impact on what areas these companies can work in, and I'm going to come back to that because it's one of the issues that I think we can address with certain changes to the way in which the HDE process is constructed and is under view with FDA. Again, very, very small populations.

So, on the HDE side -- and I'm going to have a slide that'll elucidate this in a moment -- but humanitarian device population is less than 4,000 patients a year. Well, if that's the total population that you can treat, imagine that many of these populations are quite a bit smaller than that and, therefore, are very dispersed across the population. It makes it very difficult to study them. It's -- single patients or maybe a very small group of patients who are being treated in a center for some of these diseases and, therefore, it makes it very difficult to do really well-structured clinical trials. We need different styles of trials and different ways of capturing information and accepting that information. We're going

to talk about that as well. The HDE limitations, as I said, I'll talk about, and then the fact that there is a distinct difference between the incentives that are in place for orphan drug products versus humanitarian device products are impressive, I think, and very impacting.

So, the market size, these are not commercially viable; this is not an area in which companies work to make money. This is an area -- because of the small size of the populations, an area where people invest their technology because the populations are in need, and frequently, it is technology that is being developed for other populations and can be adapted in very specific ways through design and adjustment to meet the needs of special populations, whether that is a pediatric population where we have the challenges of size and growth and development and change, or we have the situation where it's a very rare disease but different by physical location in the body, but it can, in fact, be treated by a technology that may have been developed for another organ or another organ system but needs to be modified for this small population use.

As I mentioned, the size of the population makes it very difficult for them to be studied, randomization is hard when you haven't got a large population, and when that small population has already failed, all of the things that are currently available for them. Many of our humanitarian devices have, in fact, as their criteria that patients will have failed three or four or five other therapies before they're even eligible for the humanitarian device, and in studying them, that's a very difficult population then to randomize. Randomize to what that would be appropriate, ethical, and that patients will sign up for, so it's very difficult to get patients to enroll in those studies.

In the pediatric arena, our challenge is that many of the devices are, in fact, available for adults. They are, therefore, available to be used, jury-rigged in many cases for use in the pediatric population, and getting -- again, having parents enroll their children in trials that are randomized, where they're not sure they're actually going to get a new therapy, is a very difficult problem for the patients as well as for their families.

Another set of issues on the HDE limitations is that many insurance companies consider the Humanitarian Device Exemption, even though it is an approval, to be an investigational product, and, therefore, these products are not covered by insurance, so they're not reimbursed, and that puts the patient population into a much more difficult situation in terms of their being able to access these technologies.

From a company perspective, there's very little incentive other than the desire to help to be able to take these products through to commercial sales, again, because it is considered investigational, even with an HDE. We're going to talk a little bit more in a moment about the specific incentives, things like tax and so forth that don't exist for HDE. And the standards for approval, the issue of making sure that on the device side, all of the opportunities to use valid scientific evidence, not just a large -- or not just randomized control trials, but there are many different models of data gathering that need to be considered particularly for these very, very small populations.

As I mentioned, the difference -- there are great differences today in the incentives that are in place and the support in place for a device company developing a humanitarian device versus orphan drugs. First of all, the populations, as I mentioned, are very small.

There is no exclusivity; that's common in the device arena, for those not familiar, that we don't have an exclusivity provision because the technologies tend to be -- there are lots of different kinds of technologies being developed differently for the same intervention, so exclusivity is not in the base law. Here, there might be an appropriate way to use exclusivity as a carrot for the development of these technologies. Many of the really inventive technologies are going to come from these very small companies I spoke about, and they need incentives in order to be able to spend their time and their energy and their dollars on developing these products. So, if there was real exclusivity for at least orphan products, that might provide some of that incentive. There are no tax credits, so there's no tax benefit as there is for pharmaceuticals.

For an HDE for a small population other than pediatrics, the company can recoup its development costs but not make profit. And that limitation becomes an issue when you've had a product in the marketplace over a long period of time, and I'm going to speak to that again in terms of being able to move from HDE to PMA, from a nonprofit situation to a profit situation where pathways are needed. But if you still have that very small population and you don't have the capacity to develop the kind of data that will support a PMA, maintaining a product in the marketplace, once you've recouped the original development costs, is, in fact, a challenge, and one of the issues that many companies who have had HDEs in the marketplace now over the last five to 10 years are beginning to face, and that is going to be an impediment to continued availability even for products currently under HDE. So, that's another challenge and risk that I think FDA clearly needs to address.

The criteria for the threshold for an HDE approval is safety and probable benefit. I think that you can understand why that's different, why it's not full safety and effectiveness, although safety is critical for all of these products; probable benefit, again, because the difficulty of doing full effectiveness or efficacy studies in these very, very small populations is a significant challenge. But there needs to be enough clinical evidence to show that there is benefit and it outweighs -- it outweighs risk, at least to the extent that you can tell from small data sets. And there is no specific path to be able to take, as I said, these products with either surrogate markers or other types of approaches into a full PMA approval.

The regulatory tools can, in fact, we believe be applied in different ways that CDRH could do to address these needs. First of all, there are flexible regulatory models. There is already, in the statute on regulations, the flexibility for what is defined as valid scientific evidence to support approvals. We can, in fact, improve the HUD and HDE programs, and I will speak about that and, in fact, the communications.

I'm going to come back to custom devices. One of the issues that is not addressed that really needs to be addressed is we're talking about very small populations. Well, 4,000 is small, but in many situations, we're talking about even smaller populations, hundreds of patients a year, and there is no pathway for those patients. If it's hard to develop the technology and do the testing, do the design, do the materials evaluations, and so forth, for small populations, even 4,000 a year, imagine what that's like when there are 100 patients a year, and the need to modify products, do that kind of testing, and gather some

clinical information. We believe that there's a mechanism that CDRH could, in fact, look at those even smaller populations.

I'm not going to read through, but reasonable assurance of safety and effectiveness as defined has a lot of different kinds of clinical trials that can be done, and we believe that, that's -- that, that needs to be fully used by the program, particularly for these small populations. Benefit risk is not -- should not be just this device. It's benefit risk and the disease risk and the benefit of other therapies, for these populations, we need to look more broadly than just the product in front of us and understand how that product's benefit and risk as we understand it fits into the full panoply of what's available for them and really take that into consideration as we move products forward. These may not be perfect, but they are highly needed, and we need to pay attention to that.

Again, the types of different scientific evidence that can, in fact, be used, and in the device side, something that is less familiar to those who work on the pharmaceutical side, and that is that bench and animal testing can go a long way with medical devices, particularly where we're talking about devices that may already be -- technologies that may already be well-developed in other uses, where a lot is known about those uses, and being able to do the kinds of bench testing and animal testing that can go a very long way toward understanding what the benefits and risks will be, the durability, the biocompatibility, and any other issues that might face special populations, and be able to do a lot more in the preclinical side than is possible with pharmaceuticals.

And I think this has not been used as much as it could be for HDE and HUD, particularly in the area where medical devices don't stay static. In fact, many of our products are changing within 18 to 24 months of their initial approval. This is an ongoing process. I'm fond of saying that engineers don't know how to stop tinkering, but the fact of the matter is is that devices keep evolving and getting better over their lifetime, so it does not -- we don't freeze design forever. We freeze design, get an approval, and then the design is changing again, not just the methods of manufacturing. And if, in fact, every time those changes are made, one has to go back and reconfirm that in the clinic, you can see small populations which we have problems with in the first place, even smaller populations getting exposed to the device, if you make changes and need to go back to those populations, you can see how this becomes a very, very difficult situation and, in fact, impossible to have, then, the devices evolve appropriately for these populations. So, there needs to be an acknowledgment of what can be done at the bench as well as what's then critically needed to be confirmed in the clinic.

Other populations can, in fact, be extrapolated. As I mentioned, many of these are products that have been approved for other uses in other body systems and in other patient populations. A lot of the information can be analyzed and applied to small populations, particularly pediatrics, but even the populations with rare disease, to understand the disease, understand the difference between the populations, take what can be assumed from these devices, and then understand more carefully what questions remain, and be very specific about what kinds of data are needed to address those very specific questions so that it's not redeveloping the entire product but really a focused issue. And that's very -- that could be very beneficial to moving more products into availability for these populations.

We've already talked about the types of data and the kinds of -- the clarifications that we're talking about are: How do we communicate more broadly to particularly entrepreneurial companies and investors -- and investigators for the inventors to understand what the thresholds are, what kinds of information are available to encourage more literally inventors and small companies to work in these areas? And that's critical to have much more clarity and much more visibility from FDA to companies that are not used to working in this arena.

Again, one of the areas that I think could improve is having more accessibility of experts to the process, using the clinical community who is more familiar with these products into the process, both during development as well as approval, not just as a panel to evaluate a product at the end of its development, but really to provide good information to the regulatory environment about what the benefits and risks and issues are for these specific patient populations so that it's much clearer, and working between the clinical community, the inventor, the innovative community, and the agency could go a long way. We believe that it would be very useful to have someone dedicated to pediatrics and rare diseases in the Center for Devices to be able to do some of that communication and to have a single point of contact for companies to ask these questions -- this is different than the standard development -- to be clear about the application of the predictable requirements.

One of the issues that comes up frequently for small companies -- and again, as I mentioned, many of these devices are going to be developed by small companies -- is really understanding the predictability, having a predictable process, knowing what it's going to take. What are the requirements? What are the thresholds? What are the timeframes? What can they expect from the agency? What's the process for review going to be? What's the process for development going to be? All of that is critical for small companies in order to plan and become engaged in this process, so they know the beginning, the middle, and what they can expect at the end, so they can move these programs forward.

I mentioned the issue on moving from HDE to PMA, currently trying to take data from these very small populations, very small studies, and sometimes a variety of different areas, and package that in a way that can pass the PMA threshold is a very big challenge, and whatever work can be done to clarify what's really needed, and again to focus on what is the data? What is the specific question that's unanswered to be able to move from HDE to PMA? Again, particularly where an HDE has been in the market for a while and is reaching that point where they've recouped the development costs and you're now in that no man's land, you can't make any money and yet you don't have a large enough population to do the kinds of trials that support PMA. We need to understand that better and FDA needs to address that transition in ways that would be helpful, and again, provide incentive for small companies to move into HDE knowing that they could then move to PMA, move into a profit situation, and move into a more accessible population. That's very important. And then we believe that these products should be expedited and not go through a long process, but really get the kinds of attention that an expedited PMA get from FDA.

I'm going to talk a moment on custom. For those not familiar, there is a custom provision in the medical device regulations that allow a device to be developed and used in a single patient for the very specific need of that patient, and it does not go through an approval process. So, a device can be created to meet the needs of -- I think the easiest to understand example is a patient who has a very bad accident and the kinds of injuries they have are not addressable, the kinds of defects that they have are not addressable with currently available technology that's marketed. Companies can work with physicians and create the special products, the special implants, the special approach for that given patient. But that's a single patient. We have many populations that are very small, that are 100 patients; that are 25 patients a year that need to be taken care of. To do a full development program for that small a population is really an impediment for many companies. That's just -- the kind of work that you need to do to support an HDE is more than one can reasonably expect for a population of 10 or 20. And we don't have anything in the middle. We have four single patients. We have for less than 4,000 -- well, you know, if you're in the thousands, maybe you can move that, but for much smaller populations we need an approach that can work.

We're not talking about not having an evaluation that looks at appropriate development and testing for those products, but there needs to be a pathway that allows both FDA to be comfortable and for companies to be able to move forward to meet the needs of the clinicians and the patients who are otherwise searching for and creating their own approaches. And we believe that it would be much better to have a standard evaluation of a technology and a way of understanding what those technologies are rather than every individual physician and patient creating something different. So we think there's a need here that's not being met.

That jury-rigging is a -- if you talk to anyone in pediatric medicine, they'll tell you they jury-rig all the time. We believe that there's got to be something that can be done to take that jury-rigging out and allow the people in the industry, the inventors, the technical and engineering skills to be applied to these patient populations in a way that would provide more oversight and more information than is currently available, but it needs to be somewhere less than the full HDE because, again, that's just a huge impediment. So, we believe that this is another area that should be addressed as you go forward, and looking at how we can, in fact, both develop and approve and have FDA oversight for products for these very, very small and very important populations where we understand the disease, we understand the patient population, and that their problem is that there are too few of them to be studied adequately to meet the thresholds for PMA and sometimes for HDE. So, I urge you to look into what can be done for those much smaller populations as well.

The other population that we need to talk about just briefly is the population -- okay, 4,000 is the limit. What about a population of 5,000, or 6,000, or 7,000 patients, and how do we understand what happens in that environment? They face the same kinds of issues; 4,000 was, in fact, a chosen number; it wasn't based on a lot of analysis; it was a selected number, and, therefore, there should be a process that can change that number where appropriate and still apply HDE versus PMA where the needs are appropriate. And we think that's something that clearly needs to be addressed.

I've already spoken about those three items.

Incentives would be very important. Again, just to reiterate: the tax incentives and other incentives that would allow small companies, these very entrepreneurial and innovative companies, to address issues for special populations; expediting the review; again, predictability in the program, that they would have that kind of expedited attention and would be able to move more quickly through the review programs and get to the marketplace; and then the issue on reimbursement. As I mentioned before, insurers believe that these are experimental devices and that they are not approved, and therefore are resistant to paying for them, and FDA and CMS and other insurers may be able to work together to clarify that this is an approval, that these are, in fact, well-developed and well-understood products, and that these patients, therefore, should have access and the ability to be treated and not be discriminated against by insurance policies that consider this investigational work when it really is an approved product. And as I already mentioned, some way of dealing with the HDE cap when we're talking about maybe 1,000 more patients or a few thousand more patients, and not hundreds of thousands more patients.

And with that, I thank you for your time and attention, and hope I've been able to provide you some food for thought.

Timothy Cote:

Thank you so much, Dr. Alpert.

Sixteenth Session

Open Microphone for Public Comment

Timothy Coté

I think at this point we're about to go into our open mic section, which I think has already been signed up for.

Paras Patel:

Thank you. At this time I'd like to call Shire Pharmaceuticals, please.

Ferdinand Massari:

Honored members of the FDA committee, industry colleagues, and interested parties, good morning. My name is Ferdinand Massari. I'm vice president and global head of clinical and medical affairs at Shire Human Genetic Therapies, and today I'm testifying on behalf of Shire plc. Shire's focus is to enable people with life-altering conditions to lead better lives. Through our Shire Human Genetic Therapies business and on behalf of patients and families, Shire focuses on treatments for people facing such rare diseases as Fabry disease, Hunter syndrome, Gaucher disease, hereditary angiodema and Metachromatic Leukodystrophy. Shire HGT has brought several treatments for rare diseases to patients around the world. We hope to be able to share with you today some of our experiences in the discovery, development, and delivery of treatments for these conditions. We are very pleased to testify today and thank the FDA for convening this important meaning.

As the FDA noted in its background for the meeting, rare diseases continue to pose unique economic and scientific challenges for companies that seek to provide new and groundbreaking treatments for over 7,000 rare diseases, many of which have no approved therapies more than 25 years after the enactment of the Orphan Drug Act. It's noteworthy that many of these diseases affect 10,000 or fewer patients in the U.S. and that few treatments for these rare diseases and ultra-orphan diseases have been successfully developed and marketed. The usual reviews, standards, and processes that provide the basis for regulatory success for orphan products may preclude successful development of treatments for rare and very rare diseases simply because there are not sufficient numbers of patients in the world to meet traditional review requirements. This represents a critical policy issue that affects the lives and health of 30 million Americans. Shire believe that the agency could adapt the review standards, procedures, and governance for these products in a manner that better fits the development, limitations inherent in very small, non-homogeneous and poorly understood diseases that affect these people.

Throughout our comments this morning, harmonization will be a key element that we believe will aid the development of these important therapies. In the context of harmonization, three main topics will be addressed: governance, clinical development and recommendations, and manufacturing changes.

Regarding governance, we believe that creation of an Office of Orphan Products with responsibility for review and approval of orphan therapies could help decrease confusion, maintain the FDA's high scientific standards, and help speed the development of treatments for rare diseases. We propose that the office become the primary review division for therapies for rare diseases and have access to other review divisions' expertise in a formal, regular, and expedited manner but have ultimate responsibility for the review of these products.

This new office could establish its own procedures of communication, exchange of information, consistent with the collaboration required between the agency and the sponsor. If adopted, this greater role and influence of the new office in the development of these products would assure that the products for rare diseases receive appropriate attention with a high level of insight, flexibility, and expertise. This would assure that communication with sponsors would be based on guidance, regulations, and laws that may better pertain to the risk-benefit considerations for treatments of rare diseases.

Development plans that meet global registration plans are often a must because of the very small patient populations. This office would be better able to recognize the need and would be well placed to liaise with other global regulatory authorities to understand their needs. We believe that these changes in governance could make a significant difference in the development of therapeutic products for rare and very rare diseases and would pave the way for enhancement in clinical and manufacturing development.

I would like to discuss some of the issues within the clinical development products for rare disease. Clinical development requirements for rare disease continue to pose challenges for sponsors dedicated to new treatments and are made more challenging

because of a lack of international harmonization requirements. The patient pool is simply very restricted by numbers. The need for international harmonization is exemplified by our experiencing bringing Eleprase to the market for the treatment of Hunter syndrome. The approval of Eleprase was supported by data from 108 patients, 96 patients in a Phase III program and 12 patients who participated in Phase I/II. These 108 patients were residents of 17 countries around the world. The Phase III study was conducted in four countries, the U.S., the U.K., Germany, and Brazil. These patients supported the development in really remarkable ways. One-third of them relocated from their home countries for up to two and a half years. One-third traveled by air, and the remaining third traveled by car to the study sites for their weekly intravenous infusions.

The Extension study was conducted in 52 sites in North America, South America, Europe, South Africa, and Japan to allow these patients to get closer to home. For Eleprase we were able to successfully negotiate a global development program. However, a globally aligned regulatory pathway remains an ongoing challenge for many rare diseases. It's easy to see that differing regulatory requirements only increase the challenges in conducting development programs in diseases with very small patient populations and could significantly delay the progress toward medical advancements.

We believe the FDA is well positioned to assume a leadership role and to work through and with the ICH to move toward internationally acceptable clinical development criteria for these products so that they meet very real needs. Working with key global regulatory agencies, especially in the ICH regions, to find an acceptable plan is critical for diseases in which it may only be possible to conduct a single clinical trial. Historically there have been differences between placebo-controlled versus active- or standard-of-care control requirements across different agencies, necessitating multiple efficacy trials. Cooperation and flexibility among key agencies will be essential.

As clinical development needs for rare diseases are evaluated, we call the agency's attention to the following three points that could make the development of therapies more timely, efficient, while assuring that high quality data are available to evaluate the risk-benefit ratio and support regulatory decisions.

First, the use of non-concomitant, or historical, controls: for very rare disorders, the patient numbers are so small and accrue over such a long period of time that at any given time there may simply not be enough patients available to do comparative trials with sufficient numbers of patients to meet the study objectives in an acceptable and reasonable time frame. Conducting a natural history study immediately preceding the anticipated availability of a drug can provide non-concomitant controls and is feasible. Once the drug is available, however, for clinical trials, a treatment-only trial then can be initiated. Our experience indicates that during the period when no experimental drug is available, natural history/control studies are feasible and often these studies enroll rapidly. Using non-concomitant controls as a comparative arm for a treatment trial would contribute to faster and more efficient development of drugs in ultra-orphan diseases.

Second, the use of open-label extension data: in orphan diseases, there is often understandable pressure from patient organizations and ethical committees or institutional review boards to limit the placebo-controlled portion of the study to an

absolute minimum and to proceed on to open-label extension trials. Even when the placebo effect cannot be excluded, very useful data may be gathered especially for the more objective parameters such as event-free survival and certain lab parameters. Extension trials provide for the collection of long-term safety data, which is critical given the small numbers of patients evaluated in control trials for rare diseases. These data could be used to supplement smaller controlled trial safety efficacy packages.

Third, the size of the safety database: it's impossible to gather a large safety database on patients treated for very rare diseases. Going back to the example of Hunter syndrome, 2,000 patients exist worldwide and 500 are in the U.S. A safety population of 100 patients appears very limited yet it represents approximately 5 percent of the entire worldwide population. In other disease states, the populations may be smaller still. Development of specific criteria expressed as a percentage of the total U.S. or worldwide population would be very helpful to address these considerations. If adopted, we believe that international harmonization of clinical requirements and these specific recommendations could significantly advance clinical development of therapies for rare and very rare diseases.

Now I'd like to address some issues facing the sponsor with respect to chemistry manufacturing and controls. Given the small number of patients treated and the potentially rapid pace of clinical development under the Orphan Drug Act, for many products there will be limited opportunity to develop data and experience to address some requirements of the current CMC review standards prior to approval. We urge the agency to establish clearly defined CMC requirements for therapies for rare and very rare diseases and communicate these to industry. These requirements and expectations must take into consideration and address the development and registration of orphan products, whereby accelerated clinical development is of course highly desirable but may not allow for sufficient time to optimize a commercial manufacturing process prior to completion of pivotal trials or registration, especially true for biologics.

Given the rarity of these diseases and the small patient population, a relatively small number of lots may be needed and produced to supply the entire clinical development program. This can result in limited production scale manufacturing experience and a relatively small data set to support the initial specifications, process controls, and shelf life required for registration. Especially for complex molecules, specification settings should take into the account the relatively high degree of variability and focus on critical quality attributes. With an unmet medical need, there may be a need to register the product with process validation at commercial scale still ongoing. We urge the agency to more widely and openly allow sponsors opportunities to register with a limited CMC data package that is supported by adequate scientific and risk justification. Sponsors would ultimately meet agency requirements and expectations in a post-approval setting as additional CMC experience is gained. For example, concurrent validation of the commercial process should be readily adopted for applicants for products intended to treat very rare diseases.

These recommendations we feel are consistent with ICH guidance documents where the relevant documents state, "Specification acceptance criteria should be established and justified based on data obtained from lots used in pre-clinical and/or clinical studies, data

from lots used for demonstration of manufacturing of consistency, and data from stability studies in relevant development data.

“Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use even when such batches are produced on a pilot or small scale.

“Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced. API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug products for commercial distribution based on thorough monitoring and testing of the API batches.”

To this end, the industry would be aided by agency CMC guidance specifically for development, accelerated registration, and post-approval expectations for products of very rare diseases. This would provide a roadmap for the aforementioned ICH pathways. This guidance would aid patients suffering from these rare diseases in the short term by providing access to the drugs earlier, and in the long term by encouraging and reinforcing the need for continued process and product optimization for a more sustainable supply of the products.

On behalf of Shire, we thank the agency for this opportunity to testify today. We conclude by urging the FDA to reform its governance and clinical CMC review standards for rare and very rare disease, to provide for the most efficient and effective development of treatments for these 7,000 vastly underserved conditions and the patients who deal with them every day. Thank you very much.

Timothy Coté:

Thank you for your comments.

Paras Patel:

Thank you. Next I'd like to call Sarcoma Foundation of America, please.

Matthew Aslante:

Good morning. My name is Matthew Aslante, executive director of the Sarcoma Foundation of America. We are dedicated to reform of the status quo approaches toward rare solid tumors at the FDA. On behalf of the SFA, I'm here to speak today to highlight the critical unmet need for new treatments, and accordingly, the need for a specialized, more flexible drug approval process for the many patients in this country suffering from exceptionally rare diseases such as rare solid tumors. We believe that the current drug approval process directly hinders the development of effective new treatments. Although section 314's accelerated drug approval regulations function well for the vast majority of conditions, since their adoption, it has become clear that the process is problematic for drugs and biologics intended to treat exceptionally rare diseases.

It is critical to remind everyone that the FDA has already officially addressed this matter when it comes to rare solid tumors, but it is important to understand that everything I'm

about to say about the advice given to FDA regarding rare solid tumors is directly applicable to all extremely rare diseases. From the time of the adoption of the accelerated approval regulations in the mid-1990s, it became clear that drugs approved for cancers based on surrogate endpoints were for rare solid tumors, having a tremendous problem in the capacity to perform the requisite post-marketing trials needed to confirm a clinical benefit. So the FDA called its oncology drug advisory committee together in 2005 to discuss the nature of rare solid tumors and how their affected patient populations present unique research challenges, including small population size, slow study accrual, long length of studies, evolving standards of care and treatment paradigms, identifying clinical or surrogate endpoints, and achieving significantly significant levels of evidence.

As a result of these inherent limitations, it was concluded that it is often impractical if not impossible for studies of rare solid tumor treatments to meet the current regulatory requirements for accelerated drug approval. The response from the ODAC members in 2005 were a robust range of options that could be employed to obtain data reasonably likely to show that the patient was better with the new product than without. Suggestions included scientifically rigorous epidemiological studies such as prospective cohort studies, post-marketing registry-based programs, and other observational methodologies that would provide a reasonable information to confirm that the patient's disease condition had improved. They even proposed withdrawal of FDA's current requirement of Phase IV confirmatory studies at all in the case of extreme rarity, where a large trial would be irrational to imagine.

Again, all of the [unintelligible] formal guidance was given to FDA in 2005 was from experts and not the ideas conjured up by the lay public. So how has the FDA responded to this advice from the experts? It has been mixed. In the FDA's Center for Biologics, which reviews hundreds of promising cancer vaccine and gene therapy products, cancer experts there are open and flexible. The same is true at the FDA's Center for Devices, which reviews hundreds of devices for cancer treatment and diagnosis. Similarly, at the FDA Office of Orphan Products, a great sensitivity and support has been shown towards listening to suggestions that came from ODAC on endpoints and design. Only in the FDA Center for Drugs have we found that a completely inflexible approach, the same standard for approval overall survival, has been the demand of every solid tumor approval trial done in this country. The only products that have cleared this pole vault of approval have had to have nearly curative to get through this unrealistic gauntlet. It has happened three times. Three: Gleevec for gastro-intestinal stromal tumor, topotecan for small cell lung cancer, and Nexavar for liver cancer.

The number three is the numerator. What number is the denominator? Two thousand, 2,000 rare solid tumors for which there are no treatments. Most of the FDA centers and offices have shown great flexibility and approval standards and surrogate endpoints for rare diseases, as we have heard about over these two days. But for rare solid tumors and the Office of Oncology Products, it is the same robotic refrain of overall survival, overall survival, overall survival. Whether it's breast cancer with an incidence of 250,000 or clear cell sarcoma with an incidence of 50, overall survival is the irrational and cavalier expectation for approval. This is a fact. I know of a company developing a product for clear cell sarcoma with an incidence of 50, and the company was told by the Office of Oncology Products to perform a survival trial. The same demand, overall survival for a

company developing a product for osteosarcoma, with an incidence of 900, the same demand, overall survival for another company developing a product for Ewing's sarcoma with an incidence of 600. Flexible, as flexible as a tombstone, and a tombstone is where rare solid tumor patients end up under the status quo.

So, today, the Sarcoma Foundation of America joins other groups who have spoken out to ask that the FDA develop and issue a specific guidance document on FDA's role in regulating therapies for rare disorders such as rare solid tumors, which includes an explanation and affirmation of FDA's historic position that FDA flexibly applies the standards of safety and effectiveness with respect to therapies for those with rare disorders such as rare solid tumors. I don't think we could say it any better than the manner in which the issue was stated yesterday by NORD's chairman, Frank Sasinowski. Research resources in the universe of rare disorders are precious, with the most precious being the person with the rare disorders who are heroically volunteering to participate in a trial, usually under conditions where there is less known than in trials of therapies for prevalent diseases about the safety and potential effectiveness of the investigational therapy from animal models, animal toxicology, and early human trials. So when these trials are conducted, sometimes with designs with which all parties may not be in full concurrence, including the FDA, great deference should be afforded the design of these trials and flexibility applied in the interpretation of their results. If such a principle were to be addressed and accepted by the FDA and as importantly, ensure and enforce a consistency even over rogue offices at FDA that may consider themselves above the rules followed by others, much good will come of it. We look forward to working with the agency on this very important, much needed initiative, and we thank you for the opportunity to speak today.

Time Cote:

Thank you for your comments. [unintelligible] questions from the panel?

Paras Patel:

Thank you. At this time I'd like to call BioMarin Pharmaceutical, please.

Amy Waterhouse:

Good morning. My name is Amy Waterhouse. I am vice president of BioMarin Pharmaceutical Regulatory Affairs Department. I'd like to thank Dr. Cote and Dr. McNeil for convening this important public hearing in support of orphan product development. I've personally been involved in the orphan field for many years, and I think we've reached a really interesting and exciting time where technological advances, particularly in genomics and molecular biology have enabled us to detect and understand the molecular basis for these complex diseases. This in turn has and will continue to lead to tremendous potential for finding treatments for these rare diseases, so I think it's really important that we communicate and collaborate as we are doing in these two days to ensure that the regulatory policies and procedures keep pace with these exciting and hopeful developments.

BioMarin -- I've been working with BioMarin for 10 years, and the company is very much focused on the treatment of rare genetic and serious medical disorders. We have four orphan products approved, three of which are approved in the United States. We

have three products in the clinic foyer, also for orphan diseases and most of our early stage programs are focused on rare diseases, so this is an important area that we're quite focused on. Thank you. I'm focusing on responding to question one and question four in the Federal Register notice, and I think it's important to note that there are many examples of decisions that have been made by FDA that were sensitive to the unique context of rare diseases. When we're looking across our products that are approved so far, while there certainly were delays in the development process for Laronidase for MPS I, as noted by Dr. Kakkis yesterday and I will touch on some of those issues in my further slides, pulling back, the results of our phase III pivotal study, we had two co-primary endpoints, one of which did not reach statistical significance using traditional methods of analysis. And the agency in that case pulled back and looked at the totality of the data with support from an advisory committee and approved the product based on that study.

For Galsulfase, the agency prospectively allowed the use of non-traditional longitudinal analysis, so an example of using a statistical method that works well for small patient populations. And I think the use of blood phenylalanine is another example of the agency being sensitive to the unique context of doing studies in these rare diseases.

So the question is, how can we leverage this and improve on this. And I think my focus will be the importance of providing written guidance that provides a framework for these types of decisions that will ensure transparency and consistency for orphan product developers. So first let's pull back and identify some of what we think are the most important challenges facing orphan product developers, and many of these have been touched upon so I'll move through quickly on this. But a really critical area is the fact that there is no precedent often for the use of efficacy measures relevant to the disease. There's often no therapeutic treatments for individual diseases, diseases that are very unique, and so coming up with how to measure specifically in a particular disease, improvements or the effect of the treatment is challenging. Patient populations are very heterogeneous, particularly in genetic-based diseases. There's different levels of severity based on different genetic mutations, and we've entered into development of products in rare diseases where the only literature is actual individual patient case reports. So it's very challenging to imagine designing a study with so little information.

Also we've talked a lot during this session about small patient populations. This means multi-national trials are needed. There are statistical challenges with small numbers, and as was mentioned during the Shire presentation, there's a challenge in needing to fulfill requirements of multiple regulatory agencies with a very limited number of patients. So I'm going to address each of these in my following slides.

First I believe guidance is needed in the use of novel efficacy measures. These are questions -- I've sort of put questions in this slide that come up every day for us, and it would be helpful to understand the agency's -- and obtain guidance from the agency on how to address this. So, how can we provide rationale for new efficacy assessments? What justification is needed? We've recently been asked to validate a patient-reported outcome measure in a very rare disease, and the FDA has an excellent guidance for this however it really is focused on much, much larger patient populations, so obtaining methodologies or insight into methodologies on how to apply this in the rare context would be helpful. We often ask what factors are considered by the agency to determine if

an improvement is clinically significant. So I'm talking about the size of the improvement.

Another question that comes up is under what circumstances are global assessments appropriate? Many times these genetic diseases, as I mentioned, have multi-systemic impact and so the use of a global endpoint such as clinical global impression would be very useful and we're not clear on how to justify the use of such a global assessment. I think another question is how can natural history data be used to justify efficacy measures, and just general input from the agency on how to approach the design of these types of studies to make them most beneficial. Questions that come up are should we look at a broad based cross-sectional approach or should we focus in on a smaller group of patients and conduct longitudinal assessments? In -- we've noticed that quite a few registries that are set up by patient organizations and other organizations often focus on symptomatic assessments while the agency prefers functional based. So if there was guidance around this, we might be able to create a situation where a lot of the data and effort that goes into those registries would be more beneficial and more useful to developing treatments.

I think a question that comes up is what is the value of correlations between pharmacodynamic markers and clinical outcomes? Can those correlations be used to justify the use of pharmacodynamic markers? I've gotten different answers to that question when I pose them. And I think -- I understand there's a lot of effort on the NIH side in gathering natural history data and it seems like it'd be very useful for the FDA to partner with the NIH and make sure those efforts are going -- are being conducted in a way that's going to be useful for product development.

A second area is approaches to the heterogeneous population seen in the orphan field. There's a preference for functional endpoints of course but these endpoints are highly variable; they require a large sample size in some cases and it leaves out the ability to test the drugs in very sick or very young patient populations. The six-minute walk test of course has been used successfully in many cases, but this is an example of an endpoint that leaves out important parts of the patient population. I've always thought that the use of composite endpoints makes a lot of sense, but we've run into issues related to that. There's been concerns about overlapping domains, how separate are the various domains that we're looking at; are they independent? There's also a question around the clinically significant level of improvement in a particular measure. So there hasn't been a lot of success in this, but I think some flexibility and discussion is needed because it really makes sense for orphan products.

Also in general, this has been discussed quite a lot, the confirmation of the circumstances of when orphan products can be approved by an accelerated pathway, and this leads to the question around what is reasonable likely to predict clinical benefit? I think -- I'm looking at the second bullet, the robust PD effects corroborated by strong correlations to clinical outcomes of natural history database; I would think would be supportive along with the underlying patho-physiology, also is the totality of the data relevant in making these kinds of decisions.

Also use of novel statistical approaches and study designs would be helpful to have in written guidances, affirmation of the use of these measures so that other organizations know about them and understand the FDA's perspective. And this is a question that's been posed, but I think it's worth reiterating, are there circumstances particularly in this setting where a p-value greater than .05 might be acceptable? Again, when the underlying pathophysiology is well understood and perhaps there is a strong correlations in natural history data between PD effects and clinical outcomes.

My final point, and again this has been mentioned earlier today and I'll just re-emphasize it: In order to invest in a treatment for rare diseases, it has to make sense from a financial standpoint, and this often means a company has to not only develop but also market the drug in many regions. And so I've been involved in, sort of I call the ping pong match as far as obtaining approval in the development pathway for a product. And you don't have the benefit of being able to just do a separate study for Europe, for example. You have very limited patients and so having harmonization between the requirements is really important. So I think it makes sense to think about opportunities for working with global regulatory agencies as you, FDA, think through how to approach orphan diseases. I hope that you will interact and bring some of your thoughts forward towards harmonization.

So again, there are many examples of positive risk-benefit decision made by the FDA. The importance is getting written guidance for some of those decisions. We face very unique challenges in the rare disease field and guidance is needed for orphan products and the use of novel efficacy measures, natural history data, composite endpoints, accelerated pathway and unique statistical approaches and finally global harmonization is needed to streamline development pathways for orphan products. I thank you for your attention and time.

Time Cote:

Thank you so much.

Paras Patel.

Thank you. I'd like to call up Digestive Disease National Coalition, please.

Timothy Coté:

Digestive Disease National Coalition is here or no?

Paras Patel:

At this time, we're opening up the microphone for public comment. If you'd like to speak, please raise your hand and we'll call people up accordingly. Thank you.

Miriam O'Day:

Thank you so much. Thank you to the FDA for convening this listening session, and thank you to NORD for their advocacy that ensures that meetings like this take place. I'm Miriam O'Day and I'm representing the Alpha-1 Foundation today. Yesterday you heard from a number of advocates, some of them representing themselves and their family members. Their statements were moving and I commend them for coming to address the need to enhance therapeutic development for the treatment of rare disorders, the majority of which, as you've heard, have no treatment. Many rare disorders go

undiagnosed despite symptoms and interactions with the medical community, and you've heard that there are statistics that say that from the onset of symptoms, sometimes it's seven years and five physicians before they're diagnosed, and then they get the sad news that the majority of these rare disorders lack a therapeutic solution. The HIV and surrogate marker example has been referenced at this meeting, and we should not forget that the story of HIV is one of advocacy. People laid down in the street to get FDA to take action.

To the extent possible, we should look to these positive models of advocacy and effect system change around them. We have a problem. The Orphan Drug Act has had immeasurable impact on the development of new therapies, but 357 drugs and biologics since 1983 to treat over 6,000 identified disorders is not acceptable. Each of these disorders does not have an advocate to come before you and plead their case today.

Alpha-1 antitrypsin deficiencies is a genetic hereditary condition that leads to decreased circulating levels of the AAT protein and significantly increases the risk of serious lung disease in adults and liver disease in infants, children, and adults. And Alpha-1 is the leading identified genetic risk factor for the fourth leading cause of death, chronic obstructive pulmonary disease. So somewhere between the third and fifth decade of life, individuals with Alpha-1 will become symptomatic and present and often time are misdiagnosed for a significant period of time. Testing for Alpha-1 can be done with a simple finger stick or as complex as sequencing an unusual strand of DNA. Alpha-1 is a laboratory diagnosis, not a clinical diagnosis. You can't definitely make the diagnosis based on the patient's medical history or physical examination. Diagnosis again requires a simple blood test.

The first drug available to treat Alpha-1 was a plasma-based augmentation therapy licensed as a result of the NIH's seven-year longitudinal study in Alpha-1. In 1989 the history of Alpha-1 changed significantly when John W. Walsh was diagnosed with Alpha-1 as a result of his twin brother's diagnosis. Mr. Walsh is the co-founder, president, and CEO of the Alpha-1 Foundation, which under his leadership has become internationally recognized and has invested millions of dollars to support Alpha-1 research and research-related projects worldwide. Mr. Walsh is also co-founder and president of AlphaNet, a not-for-profit disease management services company providing comprehensive care exclusively for individuals with Alpha-1. As a result of the infrastructure and support provided by the foundation and AlphaNet, two additional plasma-based therapies entered the marketplace and several companies have drugs in development for the treatment of Alpha-1, although the identified population is currently less than 7,000 individuals.

Since its inception, the stated goal of the Alpha-1 Foundation's research program was to better understand the biological link between the genetic defect and the phenotypic manifestation of Alpha-1. Early on, it was recognized that a multi-dimensional approach would best serve this goal, thus three separate but inter-related programs were created to promote basic and clinical research under the oversight of a voluntary medical and scientific advisory committee and administered by experienced staff with advice from a scientific director. The program's three major pillars have been a peer-reviewed research grant program, a DNA and tissue bank, and a research registry. The Alpha-1 research

registry is a confidential database of individuals diagnosed with Alpha-1 and persons affected by Alpha-1 who are also carriers. It serves as a resource for investigators seeking individuals with Alpha-1 to participate in clinical trials, surveys, and other scientific and medical data collection activities. We actually allow the sponsors to go through an IRB and then we send out notification to the registry participants and they respond directly to the sponsors, so there's a firewall; we do not know who participates in studies and who does not.

The Foundation appreciates the workshops that have been co-sponsored by the FDA and the NIH to advance knowledge related to specific questions in Alpha-1, and we've had a whole series of these. An analysis of the research programs' productivity and its impact on the current understanding of the biology of Alpha-1 shows that the foundation has succeeded in its quest to bring us closer to new therapeutic solutions and ultimately our goal of a cure. The \$38 million that we've invested in research to date has clarified the mechanism of Alpha-1 disease and identified novel therapeutic targets. The foundation is now in a position to promote more targeted research. The gap between basic academic research and the marketing of new drugs, the principle impediment to drug development for rare diseases, can be bridged by a partnership between biotechnology companies and voluntary health advocacy organizations. Venture philanthropy has emerged as the ideal model for this partnership by linking expertise in biotechnology with the resources of VHAs, including academic researchers, donors, and patient populations for new drug testing.

The foundation has established the Alpha-1 Project to promote this kind of research. The Alpha-1 Project, or TAP, the venture philanthropy initiative of the Alpha-1 Foundation is singularly focused on ridding the world of the effects of chronic obstructive pulmonary disease and the liver disease caused by Alpha-1 antitrypsin deficiency. The hope is that new drugs will benefit not only from patients with Alpha-1 but also expand and effect the larger population of those living with COPD. Every solution should be sought to facilitate the development of next generation therapies including the use of inhaled technologies, which today the Alpha-1 population has not enjoyed due to some problems with clinical trial design.

While individuals with Alpha-1 are struggling for breath, solutions should be found that allow the agency to be flexible and transparent in clinical trial design. We should change the paradigm to license fast and follow long.

And finally, I made a note to myself that I wanted to thank the manufacturers of plasma-based therapies. Their trade association, PBTA came before you yesterday for the work that they've done in the area of Alpha-1 and the three therapies that we have available. And they made recommendations that workshops should take place in the area of registries, biomarkers, and endpoints and we would support that recommendation. Thank you.

Timothy Coté:
Thank you so much.

Paras Patel:

Thank you. If anyone else would like to make a comment, please.

Bob Campbell:

Thank you very much for allowing me to come to the podium. I'm Dr. Bob Campbell. I'm a practicing pediatric orthopedic surgeon at the Children's Hospital of Philadelphia, and also today I represent both the Scoliosis Research Society and the Pediatric Orthopaedic Society of North America. We're very interested in this conference because we treat rare diseases for a living. I want to speak to pediatric devices. I have a special interest in that; I served as a principal investigator of a HUD device trial that was approved in 2004 with the support of NORD and the FDA Office of Orphan Products. I have a working knowledge of what went right and what didn't go so right during those years, and I'm very encouraged by the interest in the FDA in improving things for children's devices. I'd like to give you a status report from one of the guys in the trenches.

I systematically butcher devices almost every day to make them work for children, to make them fit, to make them appropriate for the function it needs. So there's a lot of work to be done. What's been going on since the approval of the Pediatric Medical Device Safety and Improvement Act, a lot of good things. A lot of companies are very encouraged by the new changes in the HDE, a lot of interest financially. The angel investors are really interested and they're funding a lot of projects. There are some issues though. As we all know, venture capital funding of devices has gone down, not just for PD devices but all devices, so it's a problem. How would that change things? Well, you saw the ad on that presentation. One thing that might make that better is to increase the availability and perhaps raise it from the arbitrary 4,000 patients a year, and I've heard repeatedly from other colleagues that maybe 10,000 might be a better benchmark, something to think about.

There's other issues too. The review process, FDA I feel needs support. CDRH is talking about panel of experts to give advice to inventors; we have non-profit consortium that are set in place that can also give advice to inventors. But I think it's very important for companies with a good idea and some backing for a pediatric device to get some expertise up front, to design their protocols, to look at the metrics they use to identify successful outcome. And this can be set up ahead of time in a systematic fashion, rather than the way we do it now, which a company goes to the FDA and the reviewers and the company sits down and then we puzzle through these issues and reinvent the wheel time and time after again. This could be done systematically in a very scientific fashion up front and define the metrics you need for -- my specialty, what do we measure for growing [unintelligible] success? What do we measure for an artificial joint for a child? Let's think about that ahead of time so they're in place when the company comes with the idea.

There needs to be affordable pathway. The presentations I've heard today all concentrate on that, as we just can't concentrate on perfection; we've got to get something that's workable. And every one of us in the audience that treat children know we do the best we can, but it's never perfect because perfect doesn't exist. And so we need to find pathways where the endpoints, they make sense, they're valid, but it's practical. It's got to be affordable.

We guys who use devices, and I'm old guard; I have no problems about sawing a plate in two and using it on a child because I know it'll work from experience. But that just might end. That's a safety valve for American medicine for children now, because we surveyed the American Academy of Orthopaedic Surgeon Practitioners that treat children. And we asked them, how often have you used a device off-label or physician directed? About a third had. And then we asked them again, what do you think about the liability? 50 percent were concerned about the liability. On my younger colleagues, I can say, appear to be much more concerned about liability than I have ever been. They might stop using this safety valve mechanism for children, which means there's no devices to treat them for an indication. As was mentioned earlier, sometimes you may have a trauma, you need a custom device where you have to take something off the shelf and modify it. But if you're not willing to do that, what's the family supposed to do?

So it's a time bomb. I think a lot of these issues can be solved by honest, open dialogue like we're having here today. But I think we also look at radical things. One thing that might be good for pediatric device development for rare diseases in children is to consider a research platform for the United States that's based on the cancer clinical trials network currently in place, Children's Oncology Group, which supports clinical trials throughout the United States, and this could help complement the non-profit consortium currently in place. We need multiple points of support; there's no one answer for this. We need to nurture inventors. We need to help them get designated as treating an orphan disease so they can have access to the HDE provision and experts. And there's a lot of volunteers willing to take their time to spend time with the FDA to try to give them insight to these issues and guidance so that we can reason out the best way to make things work. But we've just got to make things work and it's the best thing for the kids, because if we don't make things better, they're just going to get worse. I appreciate the opportunity to talk about these issues and I thank the panel.

Time Cote:

Thank you, Dr. Campbell. Good to hear from the trenches.

Paras Patel:

Thank you. The floor is open for an additional speaker.

Timothy Coté:

Others who'd like to comment. Welcome back, Dr. Kakkis.

Emil Kakkis:

Hello, Emil Kakkis with the Kakkis EveryLife Foundation. Obviously I spoke yesterday, but there are a few points that I didn't touch on that I think would be useful to mention, particularly since you're writing a report to Congress. One of the things that's come up in the last couple of weeks is this issue of foreign clinical trials and how suddenly this is a danger, and I'd like to point out that in the rare disease area, that having international or global clinical programs are essential to successful execution. And in many cases, the United States is not the best place to do the study because the health system is very fragmented. In many other places, particularly genetic disease patients, are congregated at centers and are organized and it's actually far more efficient to go to a center in

Germany that connects up and covers a wide area of Germany, whereas in the U.S., that doesn't happen. And so I think it's important if -- and you have to write a report obviously for Congress, that there would be -- and I would bet that many of the companies would agree with that 100 percent, that it's absolutely essential that you do not downgrade the value of ex-U.S. data in an orphan drug program; it's absolutely essential.

One other thing I want to talk about is pharmacology toxicology. There hasn't been that much discussion of it, but it has been potentially a problem in a number of programs, and I know a number of people have called me in the last year who've been stopped dead in the water because of pharm-tox requirements. And for many rare diseases, the amount of investment required to do a full ICH guideline small drug, small-molecule type tox program is too much money to be able to get through. And what we've noticed in time, since the time that CBER and CDER, the well-characterized biologics area was shifted from CBER into CDER, there's been a loss of the toxicologists that were really from CBER, very few of them remain and now CDER staff primarily manage that.

And we've seen a shift away from, particularly for proteins, which are very important in genetic diseases, from applying the ICH guidelines appropriate for protein therapies, replacement therapies, and a shift toward using small molecule guidance before entering the clinic. Now that results in a substantial delay in time and a substantial increase in cost. And it becomes a major factor in what companies do, and we were involved - in fact, took the program outside the U.S. for this reason, at least the first study, because of that requirement. And I think they need to make sure that, when looking particularly at rare diseases, that they're applying those ICH guidances with the appropriate flexibility those guidance's do recommend and that protein therapy, particularly replacement therapies, are given the appropriate -- appropriate guidance is being applied in those situations. And I think it's quite important for a lot of programs because of cost factor and the time factor is quite large.

The other thing related to pharm-tox is that there have been a number of situations where we're dealing with very ultra-small situations and one I had to deal with was a program to do intrathecal therapy and MPS6. And in that case, there's only about 50-some patients in the United States on this therapy. And a small fraction, maybe 10 or 15 percent, have problem with cord compression, which means only five or six patients. Now, I was able to convince the company when I was employed there to do the study to try to help them prove that problem, which only affected a relatively few, but it was a significant problem. It's not an economic benefit to the company to do it; it's just doing the right thing for patients. In that situation, we had done animal studies that were reasonable in models, but we ended up having a requirement to do a full-length monkey-tox program which would have cost more than the whole clinical program to do, and delayed us again another perhaps a year and a half.

And that's a situation where the risk-benefit of the situation, there needs to be some flexibility in the pharm tox area and that's something that I think should be looked at particularly for ultra-rare disorders, understanding number of patients exposed, risk, what data was obtained. And in many of our programs, we've had just animal model studies and entered the clinic, and I think that was an appropriate decision. Lately it seems like

it's shifted away from that and I think it's something to be looked at because I think what it had ended up doing is that program ended up being cancelled. And instead of doing a company-sponsored, carefully done program, it's now being done by investigators randomly and we lost the opportunity to do something in an organized way.

Last thing I want to talk about is the grant program, which I didn't mention. And lately there's been a number of initiatives and a lot of money going to -- or that will be going to different initiatives -- the trend initiative that provides funding for programs working with NIH. Then there's the CAN, Cures Acceleration Network, which now provides grants as well. And I'd want to make sure that the Orphan Drug Grant program is not lost in that as another piece, that shouldn't be considered one or the other, that the Orphan Grant Program should also be another piece of the puzzle; it fits a different niche and I think it should be doubled, and I think it's something that should be done in the context of the rest. But it's difficult when people see money going in these other programs to understand why those don't substitute for the Orphan Drug Grant Program. But I don't think they do and I think the fact that the money has been flat for that program, it's around 14 million, which is really trivial amount of money; it clearly should be doubled and done in the context of trying to improve the overall support for rare disease drug development. Those are my points for today. Thank you.

Timothy Coté:

Thank you, Dr. Kakkis. Do we have others in the back?

Mary Pendergast [spelled phonetically]:

Thank you very much for permitting me to speak. My name is Mary Pendergast; I have been working in the field of food and drug regulation and law for 33 years. I have my own consulting firm; I'm speaking on my own behalf and not on behalf of any client or board that I might sit on. And I didn't intend to speak so I'll be very rusty. But my first point would be that when you are looking at these small diseases -- I've heard lots of speakers say we need international trials. I'm going to ask you to be more radical and say we in the United States have X number of people with this disease. We are going to figure out what's the right therapy for those people on that basis of U.S. population. Do not compel these parents and small companies and foundations to go abroad to do their studies. Accept the fact that you have a tiny population and that you're going to work within that tiny population. So, that would be my first recommendation.

My second recommendation or statement is that the Food and Drug Administration has all the authority it needs to be wildly flexible when it comes to orphan drugs. And I think that you are choosing, not you personally, but the agency as a whole is choosing not to use the flexibility you have. I think that this may be a question of leadership, but it is a certainly a question of education. And so I would propose that until such time as you decide perhaps to have one specific division just doing orphan products, and I understand the merits of that and I also, for my fondness for the FDA, always like to think that normal review divisions can handle everything, but perhaps they can't. And perhaps rather than train all the reviewers in all the divisions to think flexibly, maybe it makes sense to have a smaller cadre of people who think more flexibly.

But I think that in the interim, while you're figuring that out, you could right a set of instructions or education for every FDA reviewer in every division from the bottom person on up, to explain what flexibility they have. You do not need placebo-controlled trials. You do not need randomized trials. You can use historical controls. If you look at Drugs, Section 314.126 has a section that says, every aspect of every clinical trial can be waived. You have all the flexibility in the world. The law doesn't say -- the law used to say or the FDA used to interpret the law that you needed two trials. Congress amended the law and said one is enough. There's since been interpretations that not even one placebo-controlled trial is necessary, case controls are fine. We approved Thalidomide based on a retrospective analysis of patient records done at the CDC, Hansen's Disease Center in Carville, Mississippi. You can use Bayesian statistics. You can use -- you don't have to use frequentist analysis. You can use adaptive trial designs. You can have letter agreements.

I was the architect of the accelerated approval program, and before we put it into regs, we would have letter agreements with companies. Because the reason why we were hesitant to take risk putting a drug on the market was because the rules for taking a drug off the market are really hard for the agency, and they take formal evidentiary hearings and about 10 years. So we invented something we called easy on, easy off, which was a letter agreement with a company that they would give us X amount of data; if it was acceptable, we would approve the product. But if later, evidence showed that the drug didn't work, they promised to take the drug off the market and not to compel us to go through the statutory scheme for drug withdrawal. That's perfectly acceptable. We then formalized that with the accelerated approval regulations. No reason why you can't go back to letter agreements, no reason why you can't change the accelerated approval regs. The other thing is you haven't changed the accelerated approval regs after Congress changed the law.

A lot of people here have said accelerated approval doesn't work because we can't do the Phase IV trials. Go look at the Food and Drug Administration Modernization Act. It gets rid of that requirement. FDA never changed the regs, but the law has changed. You don't have to compel someone to have that Phase IV trial if you don't think it's appropriate. You are scientists, you are physicians; you make the best possible decisions you can. Another thing is you don't have to have full process validation before you approve a drug. We imposed that requirement in the 90s. Go back and look to see what CBER was doing before the 1990s. In fact I'd say go look at what Marian Finkle [spelled phonetically] and Bob Temple were approving drugs on in the 1960s. The law hasn't changed except to become more flexible, but like barnacles on a boat, the requirements have aggregated and aggregated and aggregated over time. And you should remember that you don't have to impose every barnacle. You can choose not to, and what it takes is for this community and for your leadership to be willing to figure out what are the barriers you have.

You're concerned about not approving based on smaller data sets. I think one of the concerns from my years at the FDA was that everybody hated to be hauled up in front of Congress and castigated, or everybody hated to have a whistleblower colleague complain about a decision you had made. That's a leadership issue, and I encourage the most

senior people at the agency who are yours, to make the commitment that no reviewers go to Congress, they'll go and back you up. Thank you.

Timothy Coté:

Thank you so much for those comments. Do we have others?

Day 2 Meeting Close

Timothy Coté:

Okay, hearing none, I've asked Dr. McNeil to make a synopsis. Oh, you want to take a break first? We might as well just press on, right, press on and make a synopsis of the two days of the meeting very briefly. As you all know, all the comments will be transcribed and will be incorporated in the formal docket along with all of the written materials that people have submitted and the presentations themselves. So, Dr. McNeil.

Elizabeth McNeil:

First, on behalf of the committee, we would all like to thank you for coming and sharing your stories, your concerns, giving us more input as to what it was that you felt was important for us as a committee and as an agency to hear. We really appreciate that. I think that we have had the benefit of hearing from advocacy groups, from patients, from patients' families, okay. I am from New York; I am normally told that I am loud, so. We've had that benefit and I think we have a lot of things that we can take back to the committee to talk about, to try to incorporate later on into our report.

We have heard sort of major themes. One theme that we have heard is that perhaps the agency needs to make internal changes and make sure that people within the agency know, as we have just heard, about the flexibility that we do have to make changes with each application that comes in and look at what about this particular drug and this particular patient population needs to be taken into account. We have learned that it is considered very important for us to look at clinical end points and what types of clinical end points might be important to any given population. And with those clinical end points, how do the advocacy groups, how do the patients demonstrate that they are important. How do they show us that what they are seeing is what we should also be seeing, especially in chronic diseases that are progressive? Well, you may not be able to use the same things that have been used in the past. What type new things should be incorporated? And what is going to be the role of bio markers? How can we make the regulations and the review process reflect the science that's currently developing as we speak? I think we heard from Addie and Cassie's mom yesterday that, you know, there is a lot of talk but what action is being done. Well, I think that in any situation we have a sort of measured urgency as the agency tries to learn best practices.

One thing I can say is that Dr. Pariser, who, as we mentioned yesterday, was the associate director for Rare Diseases, in her less than six months that she has been in place she has managed to sort of develop a brain trust to look at different working groups within the agency and figure out, well, let's see looking at -- from statistics from pharmacokinetics, from clinical what type of things has the agency already done and where can we see improvements needed. Those are types of things that, again, the agency is looking at: What have we done, where can we improve internally, and where can we teach new

reviewers so that we can learn from what we have done in the past? We have heard that is actually something that you would like, because I think one thing that has come through is that people think that it is important that the people who are looking at rare diseases and therapeutics for rare diseases have experience and have knowledge of both disease and of the article, as the boss refers to them, that is being proposed.

We also have heard that you would like for us to look at things that are external, working on collaborations, because I think that yesterday we heard a speaker say that perhaps orphan diseases are more like each other than they are like common diseases. Well, indeed that is information that we can take and we can learn from experiences that are relevant to all orphan diseases, by working with our colleagues at NIH, by working with advocacy groups, by taking the concerns of committed individuals, because that is the only thing that really does change things to go forward and figure out how we can communicate the things that are so important to the outside and make regulatory science and make our actions reflect our appreciation of the things that are needed for patients and their families, as well as making sure that we adhere to our mandate to insure safety and efficacy, and go forward knowing that we are doing the right thing or that we've tried to do as close to the right thing as possible to make sure that people get treatments that are going to be both safe and effective, understanding that the risk-benefit analysis is different for each disease.

And trying to incorporate and communicate our assessments is something that has definitely been emphasized throughout and we are working on, first of all, this report to Congress which is due on March 11, 2011, a date that I am very aware of since I am supposed to be writing it. And I can tell you that the congressional mandate also does specifically state that internal standards, which is something that I have heard people say they would like to see, are required six months after that, so 9/11 -- hm -- but anyway, 9/11/2011 for internal standards and as well a guidance to people on the outside is due that same date, 9/11/2011. So those are some things that I have heard requested that I can tell you have already been mandated by Congress. So you will be seeing those close to those dates. I think that we really want to thank all of you who came out, all of you who sent in written comments to the docket; we are reviewing all of those. And again you will see some of the things that you said incorporated into the reports to Congress. We will be able to take some of your suggestions and incorporate them. So perhaps we will see some of them appear in the guidance document in September of next year. With that.

Timothy Coté:

Thank you. Are there any other closing comments from other members of the panel from the other centers? Anything anybody else would like to close out with? Okay, just a few on the next steps. We will be taking -- this open meeting, this public meeting, will be the topic of our next committee meeting. We will be spending a fair bit of time reviewing the comments that have come out from here. It is possible that there will be -- there may be another public meeting in the future.

As many of you know, the Institute of Medicine is due to issue a report on the nation's rare disease and drug development for rare disease policy sometime in September of this coming year. And we would welcome reflections, public reflections, on the content of that to-be-issued report. Whether those public comments will make it most immediately

into this congressional report or not is a matter of timeframe, we're not certain, but certainly we want to hear the reflections on that as part of this section 740 committee. So that will be coming -- that may be coming forward in the future. Keep your eyes to the Federal Register. Are there any other comments from anyone in this room at this time? Okay, with that, I thank everybody here for your participation, your heartfelt thoughts, and this meeting is adjourned.


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Agency: FDA

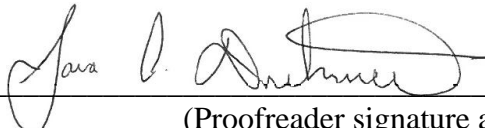
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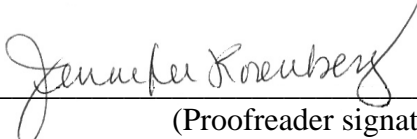
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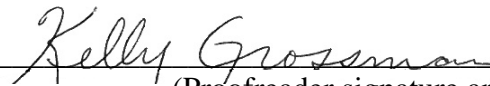
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