

1 true there have been tons of successes, and it is true that
2 there have been people harmed, both from not receiving
3 therapies and from receiving investigational therapies. In
4 the context of clinical research there is a concept known as
5 the therapeutic misconception. It is a belief that the
6 experimental procedures are directed primarily at therapy.
7 The process of science is not directly primarily at therapy.
8 It is nice when therapy happens. It is hoped that therapy
9 happens, but it is designed to create generalizable
10 knowledge.

11 Sometimes the recognition of serving as a subject
12 for someone who is sick can be challenging. The
13 phenomenology of illness, being ill, doesn't let us believe
14 that our decision-making -- that person in the white coat is
15 making a decision based on a coin flipped. But it is also
16 troublesome and challenging for investigators who are
17 clinicians who, on the one hand are trying to behave like a
18 clinician and, on the other hand, are trying to be an
19 investigator and they also fall prey to the therapeutic
20 misconception. In empirical work that has been done, both
21 patients and investigators overestimate, for instance, the
22 likelihood of any clinical benefit in a Phase I clinical
23 investigation -- way overestimate it.

24 So, this has direct implications for the informed
25 consent process. If you are being told or sold something

1 that is going to be likely more therapeutic than is
2 possible, it makes it more desirable to have it but then,
3 again, it may foreclose the possibility of other options.

4 Well, in the last few years we have witnessed the
5 range of what we call novel therapeutics -- gene therapy,
6 vaccines and biologics, and there are differences in the way
7 the trial design, the trial questions, the outcome measures
8 we can use but also in the language being employed. What
9 does that word "therapy" mean? Even a therapeutic IND --
10 therapy means it is therapeutic. It is healthful. It hasn't
11 been shown to be. It is a great scientific concept. It is
12 elegant in its design. It is stunningly important science
13 but at this time, probably in the proper terminology, it is
14 gene transfer experiments. It is an experiment.

15 Vaccines -- we take vaccines. Some folks are
16 scared of vaccines but vaccines are preventive. Cancer
17 vaccines are not preventive. It changes our notion of what a
18 vaccine is. Biologics -- they are natural. I had a secretary
19 who came in one day with an enormous rash on her face. I
20 looked at her and, you know, I tried not to overlap my roles
21 here; she wasn't my patient but she had a huge rash on her
22 face, and I said, "did you use some new soap or some new
23 cosmetics, or something?" And she said, "no, no, nothing." I
24 said, "are you sure?" "No. No, nothing." I said, "anything
25 new?" She said, "well there's this new soap we are using. I

1 got it at the natural food store." She says, "it's natural.
2 That couldn't be causing that." Well, so is a snake bite. It
3 is natural too.

4 So, the language that we use for these things --
5 biologic is natural, vaccines, gene therapy -- can change
6 our ability to communicate what it is we are trying to
7 accomplish scientifically. Does this terminology cause a
8 therapeutic misconception or add to it? It probably does.
9 There is some research that suggests it does. I don't have
10 time to share.

11 The discourse further in some of these routines,
12 and up until the death of Jesse Gelsinger last year,
13 discourse in gene transfer experiment protocols was -- and
14 this was common and there was a common parlance at meetings
15 of the recombinant DNA advisory committee -- it might help
16 but it certainly won't hurt. Jesse Gelsinger's father who
17 recently spoke at a national meeting and told Jesse's story
18 was alarmed that he wasn't aware of the preclinical studies
19 that led to what appear to be a similar toxicity in his son.
20 Although his son had agreed and had signed papers to be part
21 of that gene transfer experiment, according to his father
22 Jesse wasn't aware of the information. What he thought is it
23 might help and it certainly won't hurt, and for an 18-year
24 old kid who spent the first 18 years of his life on diet
25 control -- 18-year old boys don't like to be on a diet, and

1 as long as it wasn't going to hurt me, okays, try it.

2 So this kind of discourse contributes in some ways
3 to our therapeutic misconception and also to the press on
4 treatment abuse issues. There is enormous popular enthusiasm
5 for things that come down the pike. I recently worked with
6 some of the folks at M.D. Andersen when the endostatin
7 trials were first announced. It was an extraordinarily
8 effective agent in treating tumors in mice. Gena Colata
9 bought into it. She said this is the greatest thing. M.D.
10 Andersen received over 2000 protocols for Phase I based on
11 mice data. They had maybe 15 spots -- I can't remember the
12 exact number but that is about in the range, and how do you
13 now take something where we have traditionally said let's
14 protect you because this could be just toxic; it could hurt
15 you; you could spend your life in a clinic instead of at
16 home getting alternative therapy? How do they then allocate
17 something that was unclear?

18 Well, what are our lingering obligations? Well, no
19 surprise -- respect for persons in terms of informed
20 consent. Beneficence and non-maleficence and justice, the
21 need to treat people fairly; the need to balance protection
22 and access; getting it right.

23 In terms of respect for persons, informed consent
24 for clinical research in this area needs to recognize that
25 therapeutic misconceptions exist and take measures to

1 overcome them so that when people give informed consent to
2 trials they give meaningful and valid informed consent.

3 We need to ensure that all alternatives are
4 recognized. Just because something gets good press and good
5 adjectives doesn't mean those are all the alternatives that
6 are available.

7 Beneficence and non-maleficence, honoring that
8 fiduciary obligation that a clinician has to a patient, that
9 an investigator has to maximize benefits and to minimize
10 risks, that an institutional review board has in the design
11 of a protocol, that a sponsor has for not hurting people in
12 the process of bringing something to market -- the approach
13 here is to use alternatives that pose the potential for
14 benefit and to avoid harmful interventions.

15 In terms of justice, fairness in access, if we
16 have data that suggests this is okay make sure that the
17 access mechanisms are fair. Come up with a fair and
18 appropriate mechanism to make sure that the bureaucratic
19 issues are handled fairly and appropriately, that there are
20 mechanisms in place to help those who may not be as
21 empowered as possible to get access to things that might
22 help them.

23 This whole notion of distributing what may be
24 perceived as a scarce resource or may, in fact, be scarce
25 resource is something new to the field and needs some

1 explicit deliberation.

2 Well, in conclusion, considering access to
3 investigational agents borders on practices of medicine and
4 clinical research, raising some unique ethical issues. An
5 ethical framework provides a language with which to
6 deliberate about these issues, and the enormous reservoir of
7 trust that people still place on clinicians in a scientific
8 enterprise makes it critical to explicitly address these
9 questions and get this right. Thank you for your attention.

10 DR. NERENSTONE: Our next speaker is going to be
11 Dr. Linden.

12 DR. LINDEN: You all must be very tired. You have
13 been sitting quietly for a couple of hours, and I hope we
14 will get up and stretch soon so that some air can circulate
15 to our brains.

16 My comments will be brief, I hope, and much of
17 what I have to say you will have heard reverberations of in
18 other talks and I hope that my comments will bring things
19 together for you and offer a different kind of framework for
20 thinking about the issues that we are here today to discuss.

21 I am Ruth Linden, and I am very happy to be here
22 today. I particularly want to thank the FDA and Patty
23 Delaney and Dr. Grant Williams for inviting me to
24 participate in this meeting, and I also really want to thank
25 the public speakers who have offered crucial and incisive

1 insights, as well as the painful stories, to our
2 deliberations.

3 I am Director of Curricular Performance, Stanford
4 University School of Medicine, which means that I am
5 intimately involved with the training of generations of
6 medical students, and I am also on the faculty of the
7 Department of Family and Community Medicine at UC San
8 Francisco. I have been conducting research on policy issues
9 in the breast cancer arena and working with treatment
10 activists since the early 1990's. I am by training a medical
11 sociologist and a bioethicist.

12 I was invited to speak with you today about my
13 experience as bioethics advisor to a group of community-
14 based activists associated with ACTUP Golden Gate and
15 assisted by Project Inform. Both are San Francisco based
16 AIDS activist organizations. The group negotiated with
17 Genentech, Inc., about whom you heard earlier, to implement
18 an expanded access trial for a novel, non-cytotoxic therapy
19 for advanced breast cancer.

20 Now, as you know, an expanded access trial is an
21 entirely different mechanism from a single-patient treatment
22 IND. Even so, I believe that the Herceptin experience may
23 offer a valuable insight as we think about treatment INDs
24 this afternoon.

25 I would like to begin with a brief description of

1 the development and implementation of the expanded access
2 trial and, in contrast with most or all of what you heard
3 this afternoon, the story actually has a positive outcome.
4 So, it is a bit up, I am happy to say.

5 Expanded access arms are by now routine in HIV
6 AIDS clinical trials. However, this is not now, and has
7 never been the case for clinical trials in cancer. Thus, in
8 1994, when I began working with this group of activists this
9 coalition of community folks, community activists, came
10 together to pressure Genentech to offer a compassionate
11 access program. Herceptin, the name under which the product
12 was eventually marketed, was the first biological therapy
13 used to successfully treat some forms of metastatic breast
14 cancer.

15 As many of you know, Herceptin was approved for
16 marketing about two years ago, in September of 1998. The
17 "Her Too" activists, as I call them, were greatly influenced
18 by the highly successful approaches to treatment activism
19 developed and deployed by AIDS activists. Expanded access is
20 among the most notable reforms brought about by and through
21 the efforts of AIDS activists.

22 The Herceptin expanded access trial, in which more
23 than 700 people received therapy, was an extraordinary feat.
24 Utilizing the direct action approach pioneered by ACTUP, the
25 "Her Too" activists attempted to begin face-to-face

1 negotiations with senior staff at Genentech. Their efforts,
2 however, went nowhere.

3 In December of 1994, to press their demands the
4 activists held a demonstration with civil disobedience on
5 the Genentech campus, in south San Francisco. The next month
6 Genentech agreed to negotiate with them.

7 Negotiations continued periodically, yet the
8 company stood steadfast in its refusal to consider any form
9 of expanded access. Over the course of many months the
10 activists devised a publicity campaign to press their
11 demands for expanded access and finally, in August of 1995,
12 Genentech agreed to implement such a program.

13 The trial offered 25 slots per quarter, or 100
14 slots per year, to women who met the entry criteria. The
15 names of those who qualified for Herceptin were entered into
16 a lottery. Every month lottery entrants competed against a
17 computer for available spots. The protocol specified that
18 clinically meaningful data would be collected.

19 Over the next two years the activists pressed
20 Genentech to increase the number of expanded access slots
21 and finally the company agreed. Through a treatment referral
22 center protocol, the company entered into an agreement with
23 the National Cancer Institute that allowed Herceptin to be
24 offered though all NCI comprehensive and clinical cancer
25 centers. As many as 100 new people per quarter, for five

1 quarters, could be enrolled in the trial, which also used a
2 lottery system. There were then two expanded access trials.
3 As I mentioned above, during a three-year period more than
4 700 women received the antibody through the two expanded
5 access trials.

6 Now, it is important to understand that the "Her
7 Too" activists pushed for an expanded access trial because,
8 in no uncertain terms, Genentech refused to offer single-
9 patient treatment INDs for Herceptin, as Jennifer Bryson
10 mentioned earlier. The company did not want to be put in a
11 position of having to respond to requests on an individual
12 basis and with the appearance of favoritism. If Genentech
13 had eventually acquiesced and agreed to offer single-patient
14 INDs a full-scale expanded access trial might never have
15 been designed. In this scenario it is virtually impossible
16 to imagine that such a large number of people would have
17 gained access to Herceptin outside of Phase III trials.

18 For the "Her Too" activists the goal of the
19 expanded access trials was, of course, to provide treatment
20 options for desperately ill people. But in the back of their
21 minds, they had a larger vision, to transfer the
22 technologies of large-scale expanded access from the world
23 of HIV AIDS into the world of cancer clinical trials. They
24 believed that expanded access, run in parallel with
25 conventional clinical trials, was the simplest, safest and

1 most compassionate, just and rational way to offer an
2 unlicensed therapy to people who have exhausted their
3 treatment options.

4 When I began to work with the "Her Too" activists
5 I was by no means convinced that their view was correct,
6 reasonable or even plausible. Since that time, however, I
7 have become firmly convinced that they were, indeed,
8 correct. I can find no credible ethical, clinical or
9 scientific data that indicates otherwise.

10 I suggest that in many cases expanded access
11 trials could be a strategy for routinizing single-patient
12 INDs. First and foremost, they offer a compassionate
13 approach to those who have the fewest available treatment
14 options. In addition, they streamline and may hasten the
15 application process for manufacturers, physicians and their
16 patients and the FDA alike. Each time a request is made for
17 a single-patient IND the manufacturer must first agree to
18 offer the product and each patient, or her or his physician
19 and advocates, must seek approval. The manufacturer's
20 agreement is sought in the process, as you have heard today,
21 but is entirely separate from FDA approval, a process that
22 may be arbitrary and, as you heard this afternoon, is often,
23 in fact, arbitrary and that is, as far as I know,
24 unregulated by norms or even community standards.

25 For each of the involved parties the process may

1 be extremely awkward, uncertain and time consuming.
2 Manufacturers are under no obligation to offer treatment
3 INDs, and when they refuse to do so, they need not justify
4 their reasons. These circumstances are extremely unfavorable
5 to the policy-making process.

6 Successful negotiations with the manufacturer
7 occur before a single-patient IND is submitted to the FDA,
8 at which time a second formal process is initiated. I
9 suggest that a policy should be designed to streamline these
10 two separate steps, i.e., approval from the manufacturer and
11 then from the FDA. This could be accomplished through
12 several different approaches. With such a policy we could
13 look forward to conserving scarce resources, reducing
14 uncertainty, minimizing unintended redundancy and, most
15 importantly, setting a just decision-making procedure in
16 place that guarantees equal access, equal opportunity and
17 the exercise of compassionate judgment.

18 In closing, I would like to pose a number of
19 additional issues for our discussion. Sound policy is
20 necessarily guided by data. In order to make
21 recommendations, I -- we, in fact, need to know more about
22 the FDA's experience with single-patient treatment INDs, as
23 a question earlier was noted.

24 A white paper, in my view, needs to be developed
25 to answer the following questions, and I am going to tick

1 off a number of questions. How many applications has the
2 agency received during the past year? Two years? Five years?
3 How are these applications reviewed, and by whom? On what
4 grounds are some applications denied by the FDA? What is the
5 distribution of applications by cancer site and type?

6 Obviously, all of the applications that the FDA receives are
7 not for cancer but we are just looking at the cancer domain
8 right now.

9 Why are some manufacturers unwilling to offer any
10 mechanism for expanded access? How might outcome data be
11 collected on approved treatment INDs so that we can begin to
12 learn about the conditions under which this mechanism does
13 and does not make a difference, and what kind of difference
14 it makes in life extension or palliation?

15 Additionally, we need to explore how the FDA,
16 industry and trade organizations, and activists and
17 consumers can cooperate to develop policies and practices
18 that facilitate expanded access and single-patient INDs,
19 while simultaneously ensuring that the collection of
20 meaningful data in clinical trials will not be compromised.
21 There is no doubt in my mind that these two goals are fully
22 compatible.

23 A conference on expanded access could be the ideal
24 setting in which we could begin this work. The white paper
25 that I mentioned above could be distributed in advance of

1 such a meeting, whose purpose would be to set an agenda to
2 evaluate the FDA's expanded access programs for cancer drugs
3 and biologicals.

4 Single patient treatment INDs were instituted in a
5 period that was significantly different from our own time,
6 the post-genomic biotechnology era. The players in the
7 research and development sectors have changed dramatically,
8 with pharmaceutical and biotechnology companies taking a
9 leading role, and the NCI less prominent.

10 The range of therapeutic approaches from
11 antibodies, immune-based therapies and other biologicals to
12 novel drug delivery systems will continue to expand in ways
13 we simply can't imagine at this juncture. Cytotoxic
14 chemotherapy and hormone therapy are being joined by a new
15 generation of specific targeted therapies. It is incumbent
16 upon the FDA to set policies responsive to this new
17 generation of therapeutics while remaining grounded in the
18 values about which we just heard -- compassion, justice,
19 autonomy, beneficence, respect for persons and informed
20 consent.

21 Finally, the principle of informed consent must be
22 extended to include an informed and educated public. This
23 would allow compassionate mechanisms to be accessed and
24 utilized before people have become too ill for promising new
25 therapies to improve their health status and/or quality of

1 life. Does public education fall within the FDA's mandate?
2 If so, then how can it be accomplished? If not, then within
3 whose jurisdiction does it lie? At this time we are a great
4 and painful distance from reaching this goal. Thank you very
5 much for listening.

6 DR. NERENSTONE: Yes, I know we are getting a bit
7 short of time and there are a number of members who have
8 planes to catch, so I would like to continue on, before we
9 take a break, with our industry representatives. Dr. Spiegel
10 will be the next speaker.

11 Perspective from Industry

12 DR. SPIEGEL: Thank you very much. I also extend my
13 sympathies to those in the audience who have been sitting
14 for so long, and I also wish to certainly thank the members
15 of the public and I hope at the end of the day we can say
16 "we've heard you," and I certainly want to thank the FDA for
17 organizing a conference like this to share information. I
18 think as we have heard already, and I think we will hear
19 more, there is a great need for understanding of the
20 different stakeholders, if you will, who are in this
21 enterprise.

22 I was tempted, as we went around the room a couple
23 of hours ago with introductions, to say that I am Dr. Robert
24 Spiegel. I am the medical oncologist, as well as having
25 other titles behind my name today -- the Senior VP of

1 Medical Affairs and the Chief Medical Officer at Schering-
2 Plough, a large pharmaceutical company that has been
3 involved in developing cancer drugs for many years.

4 I do want to begin by saying I am speaking today
5 for myself and for my company and, although I have talked to
6 colleagues in other companies over the years and even
7 recently on this topic, I by no means am speaking for
8 PhARMA, for BIO, the organizational groups of companies, or
9 to echo a consensus statement in any way.

10 But having said that, I do want to say that I
11 mentioned my own background of medical oncology and that
12 began over twenty years ago when I was an associate at the
13 National Cancer Institute, and I think that was the first
14 time I realized, despite of going through medical school and
15 specialty training, that cancer drugs didn't come from the
16 NCI. At that time, I was on the phone asking drug companies
17 if we could get experimental access to drugs for patients
18 who had no alternatives. I then spent a number of years in
19 an academic setting as a practicing and research oncologist,
20 again talking occasionally with companies and being on the
21 other side of trying to get access and release of drugs
22 before approval.

23 Now, for the majority of my career I have been on
24 the other side of that table, and I just wanted to say I am
25 the face on the other side of that phone that many of our

1 patient advocates try to get through to. And, my real goal
2 today is to try to help you understand and help the
3 committee understand what goes on in the internal workings
4 of one drug company, but I don't think an atypical drug
5 company, when we make a decision on an individual request
6 for a compassionate use exemption or to start a
7 compassionate use program.

8 Let me say the statement I want to leave you with,
9 at least from our perspective, we think that in general the
10 present system provides an appropriate set of options to
11 address the various ethically and medically appropriate
12 requests for access to experimental drugs before approval.
13 When I refer to the present system I am talking about that
14 set of terms that Dr. Williams presented earlier that
15 include expanded access programs, and the special type of an
16 expanded access program called the treatment IND, and I will
17 be followed by Dr. Kennealey who will describe the specific,
18 recently initiated expanded access program, as well as
19 compassionate use single-patient exemption which, as Dr.
20 Williams mentioned, can either be sponsor initiated or
21 initiated by a physician.

22 Now, having said that we believe that the present
23 set of options that are available as appropriate, there is
24 no question that the issues that were laid out in the ODAC
25 briefing document as issues are very real. Pharmaceutical

1 sponsors in particular are very concerned about issues of,
2 number one, limited drug supply, and I hope during my
3 presentation I can explain that that is not a smoke screen
4 to try and deter interested patients. That has very real
5 consequences to the entire drug development process, and I
6 will explain in a subsequent slide that every company makes
7 a decision on every drug as to when they will scale up and
8 make a major investment to move from having enough supply to
9 test in a limited number of patients to have a commercial
10 facility that can provide adequate drug with a much lower
11 cost of goods to us, to move it into a commercial phase of
12 development.

13 Number two, our companies are very concerned about
14 the potential for a compassionate program to compete with
15 the pivotal regulatory drug development program that has
16 been agreed to. Although we almost always pose that argument
17 as not trying to get competition for eligible patients,
18 there is also competition for internal resources. I
19 certainly want to try and help you understand the diversion
20 that is created of resources and the incredible burden that
21 is created within a drug company once a decision is made. I
22 am not looking for sympathy but I am looking to help you
23 understand what happens when a company crosses that line and
24 says we will begin to entertain requests for compassionate
25 use.

1 Finally, companies are extremely concerned about
2 jeopardizing the safety profile of their drug in a less
3 controlled situation. Again, there were a number of
4 references earlier by speakers to the recent gene therapy
5 experience. While that didn't occur -- and I would underline
6 that, that did not occur in the setting of compassionate
7 use, I think it was a recent example of a feeding frenzy by
8 the press, trying to uncover more and more cases of safety
9 problems with gene therapy that, frankly, did result in some
10 immediate pause in studies until the FDA could be
11 comfortable and the NIH Rat Committee could be comfortable
12 that adequate protections were in place, and it did give
13 pause to a number of companies about the attractiveness of
14 immediately going forward in this area. So, unexpected
15 safety toxicity that can occur when you have a wide-open
16 program that is separate from your focused program, we
17 believe, can have adverse consequences.

18 Secondly, I would like to note that contrary to
19 the prevalent notion, we generally believe that we don't
20 learn a great deal from a true individual compassionate use
21 program. We learn a great deal from potentially an expanded
22 access program where a larger number of patients with fixed
23 entry criteria and description of the disease might be
24 treated and give us an early look at efficacy. I think it is
25 even more treacherous to think that we are going to learn

1 something about safety in a meaningful way through a
2 compassionate use program.

3 So, I am distinguishing. And, I think you will be
4 hearing from some other speakers that expanded access
5 programs do have the potential to enhance our knowledge of a
6 drug for efficacy and safety, but we generally believe that
7 a true compassionate individual exemption program does not.

8 Finally, I just want to emphasize again that as
9 doctors -- I appreciated Dr. Sugarman's framing of the
10 question, we are taught to do no harm, and I think within a
11 company the doctors who are following a drug know a great
12 deal about it. Contrary again to some allusions earlier, not
13 every company is interested in protecting its stockholders
14 and increasing its stock price. We don't want to deceive
15 ourselves about the efficacy of a product. I would venture
16 to say that in many regards, in many stages of development
17 the doctors in a company do not know more at any single
18 snapshot in time than even the FDA reviewers do because the
19 FDA reviewers get annual updates. They get sent immediate
20 adverse events that qualify under regulations, and they get
21 interim reports about the efficacy of a product but they
22 really don't necessarily have their pulse on just how
23 efficacious or lacking in efficacy a drug is in development
24 at any given time.

25 So, when we get a request we are, in fact, wearing

1 a couple of hats and one of those hats is to weigh the
2 benefits of what we think is the potential benefit to a
3 patient versus the very real risks. That is a tough
4 equation. One equation that is not so different, and that is
5 what we will get into, is that we definitely are buying a
6 lot more work for our entire organization, work that could
7 potentially divert us from getting a drug more quickly to
8 the FDA for review and to the public.

9 I just wanted to add one further complication, as
10 if there wasn't enough on the plate today. This slide shows
11 the experience of Schering-Plough over the last twenty years
12 with drugs, on the left-hand side, that represent drugs in
13 the oncology arena. They actually represent a hormonal
14 treatment, a biological and a conventional anti-neoplastic
15 drug. Each of them at some point in time did have
16 compassionate use experience that I will build on in my
17 talk, but on the right-hand side is another topic that we
18 haven't touched on, which is supportive therapies for
19 cancer, which bring their own set of issues. I really don't
20 have time and I don't think the committee today would be
21 able to address them, but I wouldn't discount GM-CSF, which
22 most people are familiar with as a hematologic support drug
23 that can be utilized when patients have low blood counts,
24 and it was an interesting issue in the development of that
25 drug because we knew very quickly -- we had a good rationale

1 from the clinic that we knew in animals it could increase
2 the blood count when we gave this drug. We knew as soon as
3 Phase I, in a very clear dose-related manner, that we could
4 increase the blood counts. And, there was tremendous
5 interest even in Phase II, to respond to requests to help
6 patients who had had a bone marrow transplant and were now
7 30 days past the transplant and still hadn't had any
8 recovery of their blood count, or patients who had a life-
9 threatening illness with infection, that we truly believed
10 we could improve but hadn't yet finished our studies to
11 demonstrate it convincingly.

12 Posaconazole is an anti-fungal compound that had
13 shown activity in aspergillosis, which is a very serious
14 fungal infection for which current therapy is not highly
15 efficacious. We are still developing it and we have evidence
16 that this is an efficacious product and we get numerous
17 requests, particularly from the investigators who are
18 involved in our studies for patients who don't qualify for
19 the study when they have a patient with a life-threatening
20 infection and nothing further to offer them.

21 This is the slide I want to spend a moment on, and
22 I call it the logistics of a compassionate use protocol.
23 This is really meant to address the pure single-patient
24 exemption, not the expanded access program but I think Dr.
25 Kennealey will next tell you how many aspects of this do,

1 nonetheless, apply to that program as well.

2 The exercise begins up here when a patient or a
3 family make direct contact to try and get access, usually
4 after going through a pretty good thicket of telephone tag
5 and referrals, and not going to the right place in the
6 company, get to the project physician. Every company might
7 call that person something different but the person I am
8 talking about is the individual physician who is in charge
9 of that drug for us in the company. That physician has
10 responsibility within the company to do all the real
11 clinical trials that are going to get assessed and,
12 hopefully, with completed studies will go to the FDA. So, it
13 is a busy person who has some major responsibilities, but
14 they are usually the best person to take the call when
15 somebody wants to request immediate access, and it usually
16 is immediate and a crisis.

17 That call can trigger a number of activities, but
18 one thing we do is we ask whether we can talk to the
19 physician. That is drawn with a couple of arrows because
20 physicians are busy people so it might be a series of calls
21 before we finally get to the physician who may or may not be
22 an oncologist. If it is not the physician, we have to track
23 down the referring oncologist.

24 There are two players who, for no special reason,
25 I left off this slide but maybe they will be added in my

1 next version. One is up here and I will leave it to your
2 imagination. Those are the VIPs, the congressional liaison
3 officers, the investors in your company who all have a
4 friend or a cousin who is the lawyer of the CEO or the
5 senator's close friend who is also putting pressure on the
6 company. The other player I didn't put here is the FDA. I
7 put the FDA down here but there is no reason for me not to
8 say that the project physician in our company could very
9 quickly begin a conversation with the FDA to say, "we have
10 received a request. What do you think?" Again, I would like
11 to echo what a number of other people have said. In my
12 personal experience I certainly would not bash the FDA. I
13 think on almost every occasion we have had a very realistic
14 discussion with the FDA about whether the stage of
15 development of the drug justifies a request at that time,
16 and we are usually in pretty good concordance with whether
17 it makes some sense or doesn't make some sense.

18 That, again, is a couple of phone calls back and
19 forth here. So, this project physician, who has been
20 identified by the family and is getting calls regularly to
21 find out where the drug is, if they agree -- if the company
22 has made a decision that we will entertain requests, starts
23 to ask for more information. As Dr. Williams pointed out,
24 the regulatory requirements are -- we call it a patient
25 synopsis. That could be a one-page description of the

1 patient and their previous treatment and their present
2 condition. It could be a hospital discharge summary.
3 Sometimes it is a three-inch hospital discharge record.

4 What we then say, if the patient qualifies, is we
5 tell the physician you have to get us real fast a special
6 type of curriculum vitae, with a 1572 form that the FDA
7 requires for an investigator, a signed informed consent, a
8 signed protocol and IRB approval. As you can imagine, if you
9 are going back to an institution that has been conducting
10 one of your trials, this isn't a great deal of additional
11 trouble. If you are going to a new site or if you are going
12 to an oncologist who only rarely has experience with
13 experimental drugs it takes a lot of hand-holding to get
14 through these procedures.

15 Once all these arrive, in our company our standard
16 procedure is that this package goes through two places, our
17 regulatory affairs group gets the package and forwards it to
18 the FDA. Again, at that point we have had previous
19 conversation with the FDA in most cases, although if we are
20 starting to do a lot of the same type of patient we might be
21 sending it to the FDA for notification and not having to
22 negotiate each case.

23 And, we have an internal management sign-off.
24 Because of this next step, which is packaging and shipping -
25 - and this is a pretty important concept which might be a

1 little different in a small biotech company that has one
2 product but in a company like ours and in any of the major
3 drug companies, we have a department of trained people who
4 follow FDA regulations for handling experimental drugs, and
5 it is not the same as going into a pharmacy and pulling a
6 couple of bottles of the experimental drug off the shelf and
7 throwing them into a Federal Express package. The material
8 that we have produced for the clinical trial is often
9 labeled for a double-blind study. It is packaged in the
10 amount that we use for the experimental clinical trial,
11 which might be two weeks, four weeks or six months of
12 exposure. We have to create a special packaging vial for the
13 experimental drug that would be appropriate for a patient
14 compassionate IND.

15 I am going to return to this but, within our
16 company, that request to have that sent out as an emergency
17 the next day competes with requests that that shipping
18 department and packaging group has for every other
19 experimental drug that we are developing. So, when they come
20 in to work in the morning, they have a long list of studies
21 that are about to start for oncology studies, cardiovascular
22 studies, Alzheimer studies, AIDS studies. They have to make
23 a decision of how much they are going to divert somebody
24 from what they were supposed to do that day to get this
25 shipment out. I know that sounds minimal, but even for a

1 single compassionate use request it is quite a diversion,
2 and when you start to run a couple of these a week through
3 your organization you can easily disrupt the entire planning
4 process for the studies you want to start.

5 What are the follow-up procedures that we are
6 committed to once we say we are going to supply one patient
7 or a number of patients with the compassionate product? In
8 our company -- this is our own SOP -- we send out quarterly
9 letters requesting follow-up to find out what happened. We
10 have an FDA regulatory obligation to file what are called
11 alert reports, that is, any life-threatening adverse event
12 or death has to get to the FDA real quickly. Again, if we
13 are not working with experienced investigators, it takes
14 quite a bit of education to make sure they understand what
15 their requirement is as an investigator to get us not just
16 the immediate report but all the follow-up information
17 possible.

18 That is what we have to do on an ongoing basis any
19 time something occurs. As you can imagine, in cancer
20 patients who are usually quite ill it is not unusual to have
21 a number of alert reports that are going to be kicked off
22 with any compassionate use.

23 Then, on a yearly basis we have to report to the
24 FDA, in what is called an annual IND report, everything we
25 know about our product, every adverse event whether it is

1 mild, moderate or severe or life-threatening is supposed to
2 go into our annual IND report. At the time we file the NDA,
3 when we tell the FDA we are now presenting all the
4 information we know for consideration of approval, we are
5 supposed to get all the information back on anybody who ever
6 received the drug. We also have a regulatory requirement to
7 retrieve unused drug. If the patient stops responding and
8 they don't want to take the experimental drug anymore, or if
9 the patient dies the investigator is not allowed to just
10 throw it away and they are certainly not allowed to use it
11 on another patient who looks about the same. So, we have an
12 obligation to track and be accountable for that drug and we
13 have to get it back and destroy it.

14 Finally, there is an interesting new twist, which
15 is what our obligation if the patient is doing well to
16 resupply this patient indefinitely? It is of interest that
17 in a recent reissuance of the Declaration of Helsinki there
18 is a clause that actually says that there is an obligation
19 to continue to provide a drug of value to the patient. So,
20 we are aware that once we make a commitment to try and help
21 a patient, if they are doing well we really have made a
22 commitment forever.

23 Drug supply I have mentioned, and won't dwell on
24 this but I do want to drive home the difference between a
25 clinical manufacturing phase to a commercial manufacturing

1 phase. There has been mention by the last two speakers that
2 we are in a new era of science. Many, many of the new
3 products being developed for oncology are recombinant human
4 proteins, monoclonal antibodies, gene therapy vectors. When
5 you are in an early stage of developing clinical materials
6 for the testing of these products, we do it at an extremely
7 high cost of goods. We are making a very small amount,
8 enough to get us through Phase I and Phase II. We have to
9 qualify those facilities with the FDA to show that we can
10 meet certain standards for reproducibly making the material
11 that is stable. So, we set up a facility that will be
12 adequate for the early studies and, at a certain point, when
13 we think it looks good and we think the Phase II trials are
14 going to be promising enough that we are really going to go
15 to Phase III, or at some point in Phase III with enough lead
16 time to have commercial manufacturing capability when the
17 drug is approved, every company for every drug has to make a
18 very critical business decision of when we are going to
19 switch to a commercial site that produces much larger
20 amounts at a much better cost of goods.

21 Having said that, in our company and I am sure in
22 every pharmaceutical company, we have many examples of drugs
23 that cost literally thousands of dollars per dose while we
24 are producing it for the early stage of trials. Again, I am
25 not looking for sympathy from the patient community, but to

1 start to produce more and more material before we know how
2 good the drug is going to be is a tremendous commitment.
3 Many companies I believe quite honestly say they just don't
4 have the excess material at an early enough stage when
5 patients might be excited because of something that was
6 presented as early findings.

7 I have mentioned the packaging and shipping, and
8 perhaps this is an exaggeration but, again, I have been told
9 in our company that if you start to send in a request for
10 more and more compassionate shipping what don't you want me
11 to ship today, because it takes the same amount of work to
12 slap labels on 200 vials or 200 doses of a drug for a
13 clinical trial as it does to get that one shipment out the
14 door for the patient.

15 I mentioned drug accountability and retrieval. The
16 second issue that I put on this slide is what I call
17 expanded access program specificity. As a number of the
18 people around this table know, this is a real-world example
19 of a drug I mentioned earlier, called, temozolomide, which
20 is a drug Schering developed and which has seen success in
21 the treatment of advanced brain cancers. In our pivotal
22 clinical trials we had very carefully selected patients who
23 went through a pathology review to document that their
24 underlying form of brain cancer was anaplastic astrocytoma
25 or glioblastoma multiforme. When our studies completed

1 accrual, and we were waiting for follow-up, and submitted to
2 the FDA, the word on the street and the word from many of
3 our investigators who had done these studies in patients who
4 met the protocol criteria was that this was a very
5 attractive drug for patients who had failed prior therapy
6 for brain cancer, and they wanted to get compassionate use.

7 We decided to respond to this request. You know,
8 we could go through the mechanics of why this request made
9 it, but we felt we had a good drug that was going to get
10 recommendation from the FDA for approval, and we set up an
11 expanded access program. I guess the watch words I want you
12 to think about here is the proverbial Pandora's box because
13 once you decide you are at the point that you can supply an
14 expanded access program for a very limited indication, the
15 question becomes what do you do with the call the next week
16 for a patient with end-stage medulloblastoma or a
17 neuroblastoma? Those are small variations of very rare forms
18 of brain cancer that weren't in our original clinical
19 trials, and is it ethical? Do we know enough medically about
20 them to think it is a good idea to make our drug available
21 for these patients?

22 This looks like a simple slide. It is a plea for a
23 simplified case-report form. This is one that I have heard
24 from peers about one of the ongoing issues, which is how
25 much do we have to collect as follow-up information?

1 The second point is, if you really do have a drug
2 that has been tested in thousands of patients do we need to
3 collect all of the expected, well-known side effects, or can
4 we create a case-report form for the compassionate use that
5 is only looking for unusual, unexpected or serious side
6 effects?

7 Finally, this is my final slide, and I think it is
8 the point we are going to be leaving for the committee to
9 discuss in the time that is left this afternoon, which is
10 what is the appropriate point in development? Some people
11 say after Phase II. I mentioned GM-CSF as an example where
12 the scientific rationale was very clear. It made a lot of
13 sense that if we saw translated into humans the effects we
14 had seen in animals, it should work; it should increase the
15 blood count. And, we did see that in Phase I. When we were
16 in Phase II we had interim results that we saw blood counts
17 improve; we saw patients clear infections. Even though Phase
18 II wasn't complete, is that a scenario and is it a scenario
19 that is generalizable that some drugs earlier in their
20 development, at end of Phase II, could be candidates for
21 such programs?

22 Our suggestion would be to avoid hard rules and do
23 allow exceptions. However, I am saying that but I am also
24 saying with trepidation what it does open up, and I think
25 that is going to be the topic for discussion later. Thank

1 you.

2 DR. NERENSTONE: Dr. Kennealey?

3 DR. KENNEALEY: Thank you very much. My name is
4 Gerry Kennealey. I am Chief Oncologist at AstraZeneca, and
5 prior to joining the industry I was a practicing medical
6 oncologist, and quite familiar with the NCI's Schedule C
7 program as I gave cisplatin to my patients with testicular
8 cancer and asparaginase to my patients with leukemia, when
9 those were available through the NCI program.

10 I realize that many of you are sitting there with
11 your legs crossed and Gary is going ahead and deleting some
12 of my slides at the moment to speed things up a little bit.

13 I think this is obvious from what we have seen and
14 heard today. Rising public expectations are clearly making
15 earlier access to therapies necessary. Patients are really
16 much better informed than they have ever been in the past.
17 The worldwide web is giving more and more information on
18 health and new treatments, new treatments in particular.
19 Patient advocacy groups, and you have heard from a lot of
20 them today, are more knowledgeable, more influential, and
21 more effective on behalf of their clients than ever before.

22 I was going to talk a little bit about treatment
23 INDs but I am going to skip right on to the main focus of my
24 talk, which is expanded access program. That is because we
25 believe that additional treatment approaches are necessary.

1 Patients with more common tumors are exhausting currently
2 available approved and experimental treatment options and
3 the sheer number of patients who meet description requires a
4 more efficient method of meeting their legitimate medical
5 needs.

6 For those of you who were here this morning, you
7 heard about a number of patients who had multiple therapies
8 for chronic lymphocytic leukemia and still had an excellent
9 performance status. You heard about an hour ago from the
10 wife of Mr. Tibbett who has had a number of treatments for
11 colorectal cancer and is still working full time.

12 Now I will go on to describe our own experience,
13 and our experience is with the drug called ZD1839 or Iressa.
14 It is an EGFR tyrosine kinase inhibitor that is orally
15 active and can be given only once a day.

16 We began our Phase I clinical trials in May of
17 1998 and just two years ago, in May of 2000, reported
18 initial activity in a number of clinical trials, including a
19 report at the plenary session. Following our presentations
20 there was a lot of media hype from institutions that were
21 involved in participating in these trials.

22 This is a montage of some of the publicity that
23 was seen in May following the presentations at ASCO, as well
24 as the presentations at AACR. Unfortunately, what happened
25 was that the media took a drug that appeared to have some

1 real activity in non-small cell lung cancer and put it forth
2 as a pan-cure for multiple cancers.

3 Our initial plan as a company, following those
4 initial Phase I and Phase II trials was to initiate Phase
5 III randomized, controlled trials which would lead to the
6 registration of the drug. But our information center and
7 various patient and professional groups received over 7000
8 inquiries about the compound between May and December. Calls
9 came from elected representatives, celebrities and other
10 high profile individuals expediting treatment with Iressa
11 now. We stopped counting when we got beyond 12 senators'
12 offices immunotherapy terms of phone calls, and calls came
13 not only from celebrities in the United States but from the
14 rich and famous all over the world.

15 There is plenty of precedence for expanded access
16 programs and I am going to skip over this since this has
17 been discussed amply by the representative from Genentech
18 and the AIDS experience.

19 I will now go on to what I think is one of our
20 most important slides, the principles that we used in
21 driving this expanded access program. At the time we made
22 the decision to go ahead with expanded access we had data in
23 only 300 patients, some of whom had received a tiny dose;
24 some of whom had received only a single dose. The majority
25 of activity that we saw with this drug was in patients with

1 non-small cell lung cancer. So, we elected initially to
2 limit the protocol, the expanded access, to patients with
3 non-small cell lung cancer.

4 We also felt, and we had such a small database,
5 that patient safety was a real concern and we were going to
6 be very rigorous in collecting patient safety data.
7 AstraZeneca is a global company, and we wanted to be sure
8 that there was equal access throughout the world. It just
9 wouldn't do if a pat in Germany could get Iressa for his or
10 her lung cancer and somebody in France of the United States
11 with a similar stage of disease could not. So, we wanted to
12 make every effort to have equal access.

13 The other principle, and this was a tough one
14 initially, was that we could not allow special cases. We
15 could not allow preference for the senator or the movie star
16 over the factory worker. We solicited and, indeed, received
17 full backing from our senior management, up to the CEO, to
18 enforce this policy.

19 Many people have referred to drug supply as a
20 potential issue. We were caught a little bit by surprise
21 with the results of our initial trials so we were a little
22 bit behind in ramping up our drug supply. So, we were
23 worried that that might become an issue and, as I will
24 mention later, fortunately, it has not.

25 The other worry that we had as a company is that

1 we didn't want any interference with our registration
2 program, which was also planned in non-small cell lung
3 cancer. This is a very important principle in terms of
4 expanded access. Registration is the best route to expanded
5 access. It is the best route for patients because it allows
6 them and their families to have unfettered access to new
7 therapies without the paperwork that is involved with
8 expanded access programs or single-patient INDs. It is best
9 for physicians because it allows them to make their own
10 judgment as to whether a therapy has benefit or not. It is
11 best for the FDA because it allows them to devote their
12 scarce resource to other new and promising compounds.
13 Lastly, it is best for us because it allows us to spend our
14 time further characterizing the compound and working on
15 other promising compounds as well.

16 These are the initial steps. We decided right away
17 that we could not have, as I mentioned earlier, this program
18 interfere with our efforts to get the drug to market. So, we
19 created a dedicated expanded access program or EAP team. We
20 actually considered moving them to a separate building but
21 rejected that as not being necessary.

22 We immediately involved the FDA Oncologic Drugs
23 Division and exchanged e-mails and telephone calls with them
24 over the month or so where we were putting the protocol
25 together. We also worked closely with Patty Delaney, in the

1 Cancer Liaison Office, who provided us invaluable advice on
2 dealing with sensitive issues concerning questions from
3 patients, questions from physicians, and also gave us some
4 background on the mistakes that other folks had made and so
5 enabled us to, hopefully, not repeat other people's
6 mistakes.

7 We also decided use a clinical research
8 organizations that is an external company that manages all
9 of the day-to-day activities, such as mailing out the forms,
10 getting in the forms, getting the IRB approvals -- all of
11 the things that take up just an enormous amount of time and
12 we just didn't have the folks internally to do this.

13 We also elected to collaborate with the National
14 Organization of Rare Disorders, or NORD, and you heard from
15 them earlier today. Again, they had a lot of experience in
16 dealing with phone calls from sick people and from their
17 families, and our internal folks, our internal call center,
18 is just not trained to do this, and we received a lot of
19 phone calls about other drugs and about other aspects of
20 this drug. So, we wanted to have a small group of people
21 specially trained to answer questions about expanded access.

22 This is the protocol we came up with. As I
23 mentioned before, we felt we had very good reason to
24 restrict the program to patients with non-small cell lung
25 cancer. We agreed with the FDA that it made no sense to

1 restrict the program to patients whose disease had failed to
2 respond or who had relapsed on standard therapy. We also
3 forbade concomitant therapy for cancer. We had absolutely no
4 data on the combination of Iressa with any of the common
5 cytotoxic chemotherapy drugs.

6 We also didn't want patients who were candidates
7 for our registration trials to be allowed into the expanded
8 access program because that would really slow things down,
9 in our view. We wanted patients to have at least adequate
10 general health because, again, we had no experience in
11 critically ill patients and, obviously, we had to have
12 informed written consent. Obviously, that is an issue that
13 has been talked about by a number of folks earlier today, a
14 really critical issue in dealing with a drug this early in
15 its development.

16 These are some of the challenges that we faced.
17 AstraZeneca employs 10,000 people in the United States and
18 any one of them could be approached at a cocktail party or a
19 soccer game with "my mother has lung cancer; how do I get
20 Iressa?" We wanted to be sure all of them knew the pathways
21 for patients and the pathways for physicians to find out
22 what they needed to know about our expanded access program,
23 really a critical issue from a public relations standpoint,
24 and also a critical issue to see that patients and
25 physicians got an answer quickly.

1 I have to say that when we started this we dealt
2 with some of the things that you heard from the patient
3 advocates earlier. Initially callers got into a loop when
4 they never got an answer, and we had to break that very,
5 very quickly because that was obviously very frustrating to
6 people and their families who were critically ill.

7 We had to develop a single informed consent
8 document that would work for everybody. Those of you who
9 have been involved in clinical trials know that when a drug
10 company sends out a consent form your IRB changes it around,
11 changes the wording, changes the format, usually adds very
12 little in terms of content but feels that they have an
13 obligation to make some change and put their individual
14 stamp on it. This requires an enormous amount of effort. So,
15 we took our consent form, showed our consent form to patient
16 advocacy groups, to the FDA, to NORD, reviewed it very
17 thoroughly internally so that we were quite confident that
18 we had a form that covered everything that was necessary.

19 We also -- and this goes back to Dr. Spiegel's
20 talk -- had to determine what data had to be collected.
21 Safety data at this point is very, very important. With only
22 300 patients who had received the drug, we needed to know
23 everything possible even though the data would not be
24 collected with the same rigor that was to be collected in a
25 randomized clinical trial.

1 These are some of our concerns. We really worried
2 about the potential impact on our registration trials.
3 Again, so far that does not seem to be happening. We worried
4 about the potential impact on submission and, again, because
5 we dealt with a separate team, the submission team is moving
6 ahead without being distracted by the expanded access
7 program.

8 Drug supply was a real issue, a real worry in
9 August and September. It looks like it is much less of a
10 worry for us now. However, the demand created by the media,
11 should we bring forth new results, could again make drug
12 supply a potential worry.

13 Equity I have mentioned before and I put it up
14 here again because of its importance. There has to be no
15 difference between the United States and France. There has
16 to be no difference between the factory worker and the movie
17 star.

18 The next question, and again this goes back to
19 what Dr. Spiegel talked about, is what about other tumor
20 types? Most or many malignancies express EGFR on the
21 surfaces of the cancer cells. So if a drug like Iressa works
22 in lung cancer, it might work in other tumors that express
23 EGFR or over-express EGFR. We made a decision that we would
24 delay expanding the program to other tumor types until we
25 had a little more information about the drug and currently

1 our plans are to convene an ethics board in the spring to
2 review this very important issue.

3 What about the future? Cancer drug development now
4 clearly operates in the public eye. As you can tell from the
5 speakers who started off this meeting, there is a lot of
6 awareness of what goes on in developing a drug from the
7 first preclinical studies in rats to drug approval. An
8 expanded access program, in our opinion, should be
9 considered to meet patient needs, particularly those with
10 advanced disease, especially when there is the likelihood of
11 a large number of patients who would want the compound. And,
12 successful programs require commitment and cooperation from
13 all parties involved, in this case the drug company, the
14 FDA, the patients, the patient advocacy organizations.

15 We do need some guidance from the FDA on a
16 number of unresolved issues. The role of these data in NDA
17 filings -- are they of benefit in terms of getting the drug
18 approved quickly, and is there a potential for early
19 registration, something, again, that was talked about this
20 morning?

21 I would like to finish by thanking what are now
22 200 patients enrolled in this program, our expanded access
23 team, NORD, the various patient advocacy groups, like
24 ALLCASE, who have helped us, Patty Delaney in the Cancer
25 Liaison Office, the Oncology Drug Division, and those who

1 have consulted on this program. Thank you.

2 DR. NERENSTONE: Thank you very much. What I would
3 like to do now is take a brief break and allow everybody to
4 get up and stretch and do other things, and come back at
5 4:05 because we are immediately going to want to start.

6 [Brief recess]

7 DR. NERENSTONE: Because we are so strapped for
8 time, the plan will be for the patient advocacy community
9 representatives to address the committee, after which time
10 we are going to open up for questions to the speakers from
11 the committee. We are going to have to save ODAC discussion
12 until our March meeting, at which time this obviously very
13 complicated and very important issue will get the time it
14 really needs to give the FDA some direction.

15 We do have Susan Weiner, of the Children's Cause,
16 who was able to make it now and she will address us first.
17 Then the patient advocacy community participants will speak.

18 MS. WEINER: Thank you very much. I will be brief.
19 I am Susan Weiner. I was the parent of the child with a
20 brain tumor who was diagnosed in infancy and then died just
21 short of his 14th birthday.

22 I am the founder also of the Children's Cause,
23 which is an education advocacy group whose mission is to
24 accelerate access to innovative therapies for children with
25 cancer.

1 I will be very brief. As we all know, the
2 successes in the treatment of childhood cancer over the past
3 twenty years really are due directly to high rates of
4 patient enrollment in high quality clinical trials that are
5 conducted through the national pediatric oncology
6 cooperative groups. Improvements in outcomes for children
7 whose cancers have not experienced these kinds of treatment,
8 positive treatment outcomes, notably those with solid
9 tumors, will depend on the clinical trial system made even
10 more robust through a partnership with the Children's
11 Oncology Group, the FDA, the NCI and the pharmaceutical
12 industry.

13 Evaluating standards for single-patient use in
14 pediatric oncology must be considered in this context. The
15 consensus of the pediatric oncology community, including
16 parents, is that the hope for curing these children lies in
17 more clinical trials that can evaluate new agents and
18 treatment regimens, hopefully, made even more available by
19 the newly unified national cooperative group and by a
20 vigorous application of the pediatric exclusivity provision
21 of FDAMA. For our children whose disease is resistant to
22 available treatments, special exemption and single-patient
23 access is really the last resort. We really have to include
24 our children in more clinical trials and make more clinical
25 trials available, and we would hope that that would be the

1 direction that all of these new development would go in.
2 Thank you very much.

3 **Perspective from the Patient Advocacy Community**

4 DR. NERENSTONE: Thank you very much. Mr. Carl
5 Dixon?

6 MR. DIXON: Good afternoon. Thank you for this
7 opportunity to speak to you about compassionate use of drugs
8 for cancer patients. I am Carl Dixon, the President and
9 Executive Director of the Kidney Cancer Association, a
10 voluntary patient organization which, for over a decade, has
11 been dedicated to helping kidney cancer patients and their
12 families deal with the physical, emotional and social impact
13 of kidney cancer.

14 As the only national kidney cancer patient
15 organization directed by patients for patients, the
16 association realized the importance of a national policy
17 encouraging efficient development of new oncologic drugs. We
18 commend the FDA for holding this important meeting to
19 discuss patient access to unapproved oncologic drugs outside
20 of clinical trials. The association believes that it is
21 important that the voices of patients and their advocates be
22 heard in this process.

23 Kidney cancer is an uncured disease. Today there
24 are approximately 200,000 Americans who have kidney cancer.
25 Each year 12,000 Americans die from kidney cancer. It is one

1 of only three types of cancer with an increasing incidence.
2 There is only one FDA approved treatment for kidney cancer,
3 the biological agent interleukin-2. Unfortunately, this
4 treatment only works in about 20 percent of the patients who
5 develop metastatic disease. The second-line therapy, the
6 off-label use of a different biological agent, alpha-
7 interferon, offers only modest promise of success. The
8 standard of care after these treatment is participation in a
9 clinical trial.

10 We are very concerned about the availability of
11 high quality clinical trials for kidney cancer patients. For
12 a variety of stated reasons, some of which are different to
13 understand, many patients who want to receive new oncologic
14 drugs in clinical trials are not able to meet the often
15 highly technical eligibility requirements. In particular,
16 many are barred because of trial designs that call for only
17 patients who have not received prior therapy or for patients
18 willing to perhaps be randomized to a placebo arm.

19 While we understand the need to make certain that
20 drug sponsors scientifically prove that their drug is both
21 safe and efficacious, kidney cancer patients, in search of
22 hope, want compassionate access to these drugs even knowing
23 that the safety or efficacious is unproven. In other words,
24 they are willing to take more risk. These are the patients
25 who seek compassionate use or a single-patient use of an

1 [Slide.]

2 Let us look at the problem of evidence of
3 efficacy. First, the original protocol did not specify time
4 of final analysis based on events or a specific data cutoff
5 date. However, in the statistical plan submitted by the
6 sponsor in November of '99, an arbitrary cutoff date of
7 March 8, 2000 was chosen for final analysis. As for this
8 date and NDA submission, there is no difference between the
9 two treatment arms with a p of 0.1255 and a difference in
10 median survival of 0.9 months.

11 Note that the data by this March date was
12 reasonably mature with approximately 80 percent occurrence
13 of events. Even in subsequent analysis with updated data,
14 unadjusted p-value has remained above 0.05 level with 88
15 percent of events already occurred.

16 [Slide.]

17 The second problem refers to multiplicity issues.
18 This graph illustrates that repeated analyses result in
19 different p-values. This emphasizes the importance of prior
20 specification of time of final analysis based on number of
21 events.

22 Per sponsor's statistical plan, March 8th should
23 be technically considered as the final analysis date. It
24 appears that the nadir p-value was reached with September
25 8th data cutoff date.

1 assistance to patients by referring them to other clinical
2 trials or, at the very least, to the National Cancer
3 Institute Clinical Trial Search Service. If the drug company
4 is simply not allowing compassionate access, they should be
5 prepared to justify that policy. Simply stating that it is a
6 matter of corporate policy is not an acceptable answer to a
7 patient with a life-threatening disease. Likewise, if the
8 FDA has a procedure or rule about when new oncologic drugs
9 may be made available, it must state that procedure publicly
10 and in plain language.

11 One reason frequently cited by both the FDA and
12 the drug companies for denying compassionate access is that
13 the single user data might be used against the company when
14 they file their new drug application. Balderdash! While, by
15 statute, the FDA must track that safety data on every single
16 patient, including compassionate use patients, if such
17 patients die as a result of their cancer, the expected
18 outcome in this group of really seriously ill patients, then
19 the data is not used against the drug company. The only time
20 that compassionate use safety data might be used is, for
21 example, when every patient on compassionate use dies from
22 an unexpected source or a remarkable adverse event occurs.

23 I am sure that the advocacy community will be more
24 than willing to disseminate this important information on
25 how to secure compassionate access for all Americans. I know

1 the association would do so. Once again, we commend the FDA
2 for assessing and reviewing this complex subject of
3 compassionate use and, in conclusion, I want to express
4 thanks to Terry Tuergo, Patty Delaney and Joanne Minor for
5 the excellent work that they do every day with patients
6 seeking compassionate use. Thank you.

7 DR. NERENSTONE: Mr. Robert Erwin?

8 MR. ERWIN: Well, I am with the Marti Nelson
9 Cancer Research Foundation. We have worked with patients
10 with a variety of types of cancers in making treatment
11 decisions and enrolling in clinical trials, getting access
12 to experimental medicine through a variety of mechanisms.

13 The comments I want to make today are derived from
14 that experience, which has varied across the map in terms of
15 both success and failure. I would like to start with an
16 observation that this rather complex issue should probably
17 be dealt with in a much more extensive analysis than we have
18 time for today, but really we can reduce it down to one
19 simple consideration that I think should guide the rest of
20 the debate, and that is that for some people suffering a
21 terminal disease treatment with an investigational drug
22 might be the only opportunity they have for an extension of
23 life. That will not be true in most cases but it is true in
24 some cases. I think if we keep that in mind as we go through
25 the analysis and consider that fact, it may guide some of

1 interpretable and subgroups have to be studied individually.

2 In such a case, one can consider subgroup
3 analysis. Since the sponsor presented Table 11b of my
4 review, I would like to clarify that this model was
5 considered to test for interaction and find a rationale for
6 further subgroup testing.

7 This model was not intended to evaluate the
8 treatment effect in either of the subgroups, that is, either
9 the liver met subgroup or the non-liver met subgroup. A
10 subgroup analysis was further performed in my review, as
11 well.

12 [Slide.]

13 However, in this study, stratified randomization
14 within liver subgroup was not done. Imbalances favoring
15 histamine plus IL-2 arm in the distribution of patients are
16 observed. Furthermore, liver metastasis subgroup hypothesis
17 testing was added on to the original protocol after the
18 study had completed enrollment.

19 No allocation of alpha for testing liver
20 metastasis subgroup hypothesis was planned prior to the
21 start of the study. A statistical plan was submitted by the
22 sponsor prior to NDA submission with a plan for post-hoc
23 adjustment of type 1 error for testing liver metastasis
24 subgroup hypothesis.

25 [Slide.]

1 In this graph, red bars represent histamine arm
2 and blue bars represent IL-2 arm. The message to be taken
3 from this bar graph is that the red bars, which represent
4 the histamine arm, have higher percentage of patients in all
5 the better prognostic subgroups. For example, patients with
6 less than 65 years of age, female, performance status of
7 zero, no prior chemotherapy, et cetera.

8 Thus, this bar graph illustrates that the
9 imbalances observed favors the histamine arm. It should
10 also be noted that of the 14 characteristics presented in
11 this graph, 13 of them favored histamine arm.

12 [Slide.]

13 Because of these imbalances in the liver subgroup,
14 it is appropriate to further evaluate treatment effect using
15 covariate adjusted analysis. Sponsor has submitted models
16 which are different models with different data cutoff dates.
17 They are also different from protocol specified covariate
18 and covariate specified in the statistical plan.

19 FDA has used consistent model at all times and no
20 selection was considered, that is, all characteristics
21 identifiable with imbalances were included in the model.

22 [Slide.]

23 In the original model, only two factors were
24 prespecified, presence or absence of liver metastasis, and
25 secondly, whether the patients received prior chemotherapy

1 any risk, and it is impossible for any group, no matter how
2 wise it is, to make the right decision for that broad range
3 of individuals varying across all sorts of situations. I
4 think that should be left to the individual.

5 However, it is very important to ask is a
6 patient's expectation of benefit realistic, or is it only
7 false hope. When we help patients to choose clinical trials
8 for enrollment, our function with the patient and the
9 patient's physician is to try to assess the probability of
10 therapeutic benefit. It has been pointed out very clearly
11 that research studies are not designed to provide benefit,
12 but patients enroll in research studies primarily on the
13 chance of receiving benefit, not as individual acts of
14 altruism to advance the experimental status of science and
15 medicine. Recognizing that duality I think is extremely
16 important.

17 The expectation of benefit is something that has
18 been a major factor, I think, in the hype and the interest
19 has in coverage by the media. It is a circular argument --
20 does the media generate the hype or does the public draw the
21 hype because of their hope that there will be these kinds of
22 benefits? There are many cases where the only likely benefit
23 that apt is likely to receive from a clinical trial is the
24 psychological benefit of participating, but in some cases I
25 think it has been demonstrated, although as people have

1 pointed out today there has not been a systematic gathering
2 of data to evaluate this, that there have been individual
3 cases of life extension and even dramatic recoveries, at
4 least for short periods of time, as a result of early access
5 to experimental therapies.

6 So, I think that it makes sense for the FDA to
7 leniently approve individual treatment INDs and to
8 distinguish between expanded access protocols and individual
9 treatment INDs in terms of the expectation of benefit. An
10 expanded access protocol is very appropriate I think for
11 promising cancer therapeutics after efficacy data has been
12 gathered in Phase II trials, and these should be based on a
13 realistic possibility of therapeutic benefit. They can, and
14 should, be designed so that they do not conflict with Phase
15 III trial enrollment. On the other hand, in cases of rare
16 cancer, very unusual situations, complex situations where
17 patients may have multiple disorders expanded access
18 protocols will not be appropriate. Patients will not qualify
19 for those either. Because it is impossible to know the
20 probability of success in these widely varying cases, I
21 think there will be a role for individual exemptions,
22 individual treatment INDs even if there is broad acceptance
23 and implementation of expanded access protocols.

24 If FDA has data suggesting a safety risk that
25 would not be known to the physician and the patient, I think

1 Furthermore, the p-values presented in the table are not
2 adjusted for multiplicity, meaning multiple hypotheses or
3 multiple analysis.

4 For example, adjusting only for two hypotheses,
5 one in the ITT population and one in liver metastasis
6 subgroup, the p-value is 0.1146 with the updated data.

7 [Slide.]

8 Therefore, the take-home message is that the
9 adjusted model results are sensitive to inclusion and
10 exclusion of a covariate. They are also sensitive to
11 whether a covariate is used as a continuous variable or a
12 categorical variable.

13 More importantly, it should be kept in mind that
14 these p-values are not adjusted for multiplicity either for
15 multiple subgroups or multiple analyses.

16 Thus, there is no robustness in the liver
17 metastasis subgroup finding, and it is not possible to
18 assess the true treatment effect in this subgroup given the
19 imbalances from one single open label study.

20 Dr. Griebel will continue the presentation
21 addressing further the single study issues.

22 DR. GRIEBEL: Good afternoon. My name is Donna
23 Griebel and I am the medical team leader. We are here today
24 considering an application that has as its foundation a
25 single randomized controlled trial, and my job on behalf of

1 unapproved indications and in patient subpopulations that
2 were not represented in the clinical trial. This is one
3 reason that certain products have so significantly exceeded
4 the sales projections of Wall Street analysts, and it is a
5 phenomenon well understood by the companies that market the
6 drugs.

7 I think the FDA has done a good job so far in
8 addressing this important issue. I hope that in considering
9 its policies the FDA will further foster a regulatory
10 environment that encourages both individual treatment INDs
11 and expanded access protocols, and I favor the FDA taking an
12 active role and outreach to make the opportunities widely
13 known and understood. Such outreach and education will
14 probably require that the FDA have additional resources, and
15 I think the patient advocate community and the public needs
16 to take some responsibility for making those resources
17 available.

18 The issue of fairness is a different one that
19 should be taken seriously, but difficulty should not be an
20 excuse to take no action. I think, as I mentioned earlier,
21 the FDA should anticipate the possibility that a new
22 generation of drugs is coming down the pipeline that will
23 demonstrate better efficacy and also generate increasing
24 demand for early access.

25 Perhaps the FDA can actively encourage the

1 development of better validated or surrogate markers for
2 efficacy to shorten the clinical trial process, and develop
3 guidelines for the incorporation of cross-over provisions in
4 Phase III trial design so that patients randomized to the
5 standard treatment arm have the possibility of benefit from
6 the new agent if standard treatment does not prevent disease
7 progression. The potential conflict between the need for
8 randomization in clinical pivotal trials and a patient's
9 desire to obtain treatment with an experimental agent is an
10 important topic for further discussion.

11 The FDA could also clarify the circumstances and
12 extent to which drug sponsors should be concerned about
13 adverse events that might occur when patients are treated
14 under individual INDs.

15 Finally, I would like to comment on my view of the
16 responsibilities of the drug developers, and I appreciate
17 very much the two presentations earlier from pharmaceutical
18 companies. I think that if we can believe what the
19 scientific, medical and corporate world tell us, then
20 dramatic improvements in the treatment of cancer are just
21 around the corner and, unfortunately, have been just around
22 the corner for the past ten years. As optimistic as I would
23 like to be, I don't believe the news is this good.
24 Unfortunately, a lot of it is just hype promulgated
25 especially, I think, and this is a little bit of a bias, by

1 smaller companies to increase interest in their stock but
2 also by others to increase the sales of newspapers, books
3 and research reports. For better or worse, the steady flow
4 of good news, both the real and the misleading, is actually
5 building a market for compassionate access to experimental
6 drugs. The same companies that frequently resist providing
7 access to investigational drugs outside of clinical trials
8 are building this market. Companies need to reconcile the
9 incongruence between the exuberant optimism they steadily
10 foster on the press and financial community with the
11 unfortunately pedestrian reality of most of their cancer
12 products' performance. Demand for compassionate access will
13 only increase as information technology, such as the
14 internet, continues to expand and the real breakthroughs
15 begins to show up in the clinic as they may be starting to
16 do already.

17 Companies must be clear and honest with the public
18 about their policies, and make it clear, if the answer is
19 no, that that is their responsibility. There are a number of
20 perfectly valid reasons that a company might choose to deny
21 access to an experimental drug but, as has been
22 unfortunately my experience in a number of cases working
23 with individual patients, companies choose to blame the FDA
24 and the FDA is, in fact, not the problem in this case.
25 Companies should take responsibility, not blame the FDA, and

1 make it very clear what the process is if the answer is yes,
2 and if the answer is no make it very clear that there is no
3 recourse by getting into this continual loop back and forth
4 between multiple physicians, possibly politicians, lawyers,
5 the FDA and others. That kind of circle of misinformation is
6 a waste of time but, most importantly, it generates false
7 hope which is a very unfortunate thing in these sorts of
8 diseases.

9 I appreciate the opportunity to address the issue
10 and hope these comments have been helpful. Thank you.

11 DR. NERENSTONE: Thank you. Our last speaker for
12 this afternoon is Miss Jan Platner.

13 MS. PLATNER: Thank you. I am Jan Platner, from
14 the National Breast Cancer Coalition, and on behalf of our
15 over 500 member organizations I want to thank you for the
16 opportunity to comment today.

17 Since NBCC's beginning nearly ten years ago, our
18 commitment to evidence-based medicine has been fundamental
19 to all of our advocacy efforts. We need to know what works
20 for women with breast cancer, and all breast cancer patients
21 need access to what works. Women with breast cancer should
22 not be given false hope by treatments that are unproven.
23 Interventions must be based on the best possible science
24 available, and the best way to achieve that is through well-
25 designed clinical trials.

1 There are all too few truly effective treatments
2 for most types of cancer. While the public is inundated with
3 information about cancer breakthroughs and news of promising
4 new drugs, the reality is that most drugs result in
5 incremental improvement at best.

6 The research process seems agonizingly slow for
7 those who have run out of treatment options, and
8 pharmaceutical companies, scientists and the media each bear
9 responsibility for creating unreasonable expectations about
10 unproven drugs. This has created a climate where many
11 patients mistakenly believe that access to an
12 investigational drug is their last hope when, in reality, it
13 is a false hope.

14 Public policy should discourage access to
15 investigational drugs outside of clinical trials. The
16 coalition believes that single-patient INDs should not be
17 granted but, rather, in situations where there is a
18 compelling reason to grant access to drugs outside of a
19 clinical trial that should be done only in the context of
20 expanded access protocols in which distribution of the
21 investigational therapy is fair and data is captured that
22 would add to the scientific base of knowledge about the
23 intervention. Expanded access should not be the norm but,
24 rather, protocols may be allowed in particular circumstances
25 and only for those individuals who do not meet the

1 eligibility requirements for a clinical trial.

2 If an expanded access program is allowed, access
3 to the drug must be fairly and blindly allocated and all
4 individuals must be followed, and their data reported to the
5 trial sponsor. Expanded access should not be allowed until
6 there is safety data available from a completed Phase II
7 trial, and data that provides some basis for determining the
8 drug may be efficacious.

9 While it is compelling to argue that there is
10 little harm in making investigational therapy available to a
11 seriously ill individual for whom there is no effective
12 therapy, if someone is willing to pay for it, this argument
13 simply does not hold up under scrutiny. To follow this to
14 its logical conclusion completely undermines research and
15 the concept of evidence-based medicine. Where does one draw
16 the line? It would mean that any individual should have
17 access to any drug as long as she is persistent and willing
18 to pay for it.

19 Investigational treatments made available outside
20 of clinical trials have the potential to undermine the
21 clinical trial system. There is little incentive for a
22 patient to participate in a clinical trial if she can obtain
23 the investigational drug outside the trial. I think in the
24 case of breast cancer, I hope, we have learned some lesson
25 from the bone marrow transplant issue where that

1 intervention was widely available before it was ever proven
2 to be effective, and we could have known years sooner that,
3 in fact, it does not provide benefit for women over standard
4 therapy. We could have saved thousands of women from going
5 through that gruelling process, and perhaps thousands of
6 women's lives.

7 Certainly investigational treatments by definition
8 are unproven, and even the most promising data in earlier
9 stages often does not hold up. Further, there may be
10 significant safety issues that do not emerge until well into
11 Phase III trials, and that was certainly the case with
12 Herceptin where the cardiotoxicity issue did not emerge
13 during Phase II trials and it was only when we had much
14 larger Phase III trials where that issue surfaced.

15 Finally, single-patient INDs raise serious issues
16 of fairness or, rather, unfairness. Patients who have access
17 to them usually are very knowledgeable. They have access to
18 physicians who have the ability to develop a protocol for
19 them and are willing and able to implement it. This is not
20 the case for most women with breast cancer. Resources
21 devoted to funding breast cancer should be allocated fairly
22 based on the best evidence available and, frankly, when drug
23 availability is an issue, as it certainly was with Herceptin
24 and it is frequently an issue, we can find no way -- we have
25 thought of no possible way where you can really make the

1 single-patient IND process fair.

2 We recognize this is an extremely different issue.
3 We all want to save lives. We must work together to develop
4 the right public policy that will achieve all that, and that
5 must include movement toward more and better research,
6 expanded clinical trials and access to healthcare for all
7 Americans. We believe that a policy supporting single-
8 patient INDs would undermine those efforts. Thank you.

9 DR. NERENSTONE: I want to thank all the speakers
10 this afternoon. I think you, all, have done a tremendous job
11 in sort of outlining the problems. We are not going to have
12 time to really get into the discussion of those problems. I
13 do want to open it time for the time remaining for the
14 committee to ask the speakers questions or clarification of
15 their presentations.

16 I will start it by asking especially the
17 representatives of the patient advocacy community, do you
18 think that we can at least start this discussion by
19 outlining who we know should not get investigational agents?
20 That is, the community cancer centers, protocols and a lot
21 of our research suggests that performance status 3 and 4
22 patients, no matter what you give them, are not going to
23 benefit from continued treatment. Do you think that we can
24 start by saying who really should not get treatment as a way
25 to at least limit our discussion?

1 MR. ERWIN: I think that is a very important point
2 and it is something that I have been very curious about.
3 There have been anecdotal reports of patients at very late
4 stage, with very poor performance, benefiting from access to
5 experimental drugs. In fact, during the Herceptin expanded
6 access program there were some very publicized, media-
7 covered, individual cases. But, as far as I know -- this may
8 be known to FDA or to Genentech, I don't know what the
9 longer-term outcome was. I don't know if people really
10 received benefit or not. The cases that I am more familiar
11 with are cases where people received no benefit and, in
12 fact, in some cases may have been harmed. So, I think that
13 is a very interesting proposal and I think in general the
14 patient advocacy community is interested in making clear
15 what the risks are. If it turns out that there is a
16 reasonably objective basis to say that risks are extremely
17 high or benefit is essentially zero, then you will probably
18 have broad support for those kinds of limitations.

19 DR. NERENSTONE: Other questions?

20 DR. PAZDUR: The industry and also perhaps the
21 patient representatives may like to speak on this, and that
22 is this concept of early hype of drugs and now is that
23 developed? You know, we have seen a lot of publications that
24 come out at ASCO with really interim analysis of data, of
25 early findings of data that come out. I guess for Gerry, how

1 does the industry view that? You know, it is a double-edged
2 sword in the sense of promotion of a drug, in a sense, for a
3 drug company. But, on the other hand, you know, it does
4 create this false hope. How is this viewed by industry?

5 DR. KENNEALEY: You have hit the nail on the head.
6 It is a very different issue, less so for large companies
7 like the Pfizer's and the Merck's, but certainly we have to
8 draw a fine line between getting the information that is
9 available into the public domain and becoming purveyors of
10 false hope. It is often not an easy line to walk.

11 DR. PAZDUR: Many times these abstracts are
12 actually presented while the trial is ongoing, some
13 preliminary level of activity is noted in the abstract.
14 People pick this up and it really becomes a very negative
15 thing when it is reported, especially if these results do
16 not hold up in the long-run and there is this creation of
17 false hope that does exist. Even in scientific meetings we
18 see this. I will just refer you to last year's ASCO where a
19 picture of a single patient was on the cover of one of the
20 publications that were circulated by that organization, a
21 single patient response of an investigational drug, which I
22 found somewhat alarming in a scientific meeting.

23 DR. KENNEALEY: Hopefully, most of the people who
24 review these scientific abstracts will have a little better
25 filter than that, but I think it is reasonable to bring into

1 the public domain early information from Phase II trials,
2 especially if there are really dramatic differences. You
3 know, there are a number of examples of that, dating back to
4 the days of cisplatin in testicular cancer. I think all of
5 us have a real obligation to keep information on Phase III
6 trials strictly confidential until there is clear evidence
7 that the endpoints have been reached or that the differences
8 between the two arms are so dramatic that a body that is
9 external to the company makes a recommendation that the
10 trial be stopped.

11 DR. NERENSTONE: Dr. Williams?

12 DR. WILLIAMS: I don't know if I used the right
13 terminology or not. I think you were talking about
14 beneficence and autonomy, and it seemed to me I was hearing
15 some conflict there, maybe some of the advocates and
16 patients were suggesting that FDA should really be in the
17 business of getting into the autonomy business. How does one
18 begin to deal with this conflict between the patient who
19 feels that they are totally informed and the FDA perhaps
20 becoming involved in the safety analysis and saying that
21 maybe there is a safety concern?

22 DR. SUGARMAN: I think you are right to point out
23 where one of the conflicts are, and there certainly is, in
24 this situation, a conflict of those principles to respect
25 autonomy and to do good by patients.

1 There are a couple of pieces, as you sort of
2 specify these principles, to do the work that they have to
3 do and in a tough case like this one of the pieces that you
4 need to understand I think is that the obligation to not
5 have things done to oneself seems to be a slightly greater
6 obligation than a request for something, for someone else to
7 do something to you. So, it is a stronger claim to say don't
8 touch me compared to the claim of I want that and,
9 therefore, I can have it. They are both claims of autonomy
10 but they seem to be somewhat different.

11 The second piece about the beneficence argument,
12 as you tried to play that out a little bit, is the argument
13 of the risk on the one hand and the benefit on the other. If
14 you tried to sort of do the math, it wouldn't work; they are
15 not commensurable, as we say.

16 I think it goes towards enhancing autonomy, and
17 one of the possible solutions would be autonomy enhancing by
18 providing accurate information about risk and what the
19 concerns are as a clinician, as an investigator, as an
20 agency, as a sponsor to understand do you know enough about
21 the risks to provide counseling? Are the risks completely
22 uncertain? Does the person know what these risks might be,
23 and how that risk assessment goes? Some people are more risk
24 seeing, other people are more risk averse, and that part
25 they retain throughout the informed consent process.

1 Likewise, in terms of benefit, clinicians and
2 investigators ought not give something that they know is
3 going to hurt someone or be completely inefficacious. So, if
4 someone asks for an appendectomy to be done because they
5 thought it would cure their cancer, they just wouldn't do it
6 regardless of how risk seeking they were. I mean, if it
7 doesn't make sense, if there are no data to support it, it
8 is not something that someone would engage in. I don't know
9 if Dr. Pellegrino wants to take this on as well.

10 DR. PELLEGRINO: Just a word on autonomy. It has
11 become absolutized. People fail to realize there are
12 limitations to autonomy, several limitations. First of all,
13 when your autonomy results in harm to some other
14 identifiable person, harm which is grave, probable and
15 identifiable so, therefore, if you are talking about an IND
16 you can see scenarios in which the demand is not
17 absolutized. That demand is limited if it has an impact on
18 others, and we could go on to scenarios for that.

19 The second one I think is the failure to
20 understand that the health professional and the person who
21 has been required to satisfy your autonomous wish or desire
22 also has a right to autonomy. And, I think we are seeing
23 here increasingly in the clinical situation, as a clinician
24 myself, a tendency to say, well, we will do it because the
25 patient wants it and particularly in pediatric situations

1 because the family wants it. They don't always act in the
2 best interest of the patient or the person who is the most
3 vulnerable member of that decision-making constellation.

4 So, I think autonomy has to be taken very, very
5 carefully and put into a context in which, first, there is a
6 balance between the autonomous claims of the various
7 individuals, particularly the professional and, secondly,
8 the impact of an autonomous choice. Then, thirdly, as Jeremy
9 pointed out, the move from autonomy which started as a
10 negative moral right -- don't tread on me -- has moved to a
11 right to demand and, as a matter of fact, in the clinical
12 situation we find over and over again a right to feel that
13 one might participate in the micromanagement at the bedside.
14 That, I think, acts very often to damage of the patient, and
15 we can't do that.

16 So, I think the whole question of autonomy needs
17 to be reexamined very carefully. Just a last word on it,
18 that is that more recent empirical studies show that when
19 patients demand autonomy they are not really saying I want
20 to make this decision by myself; leave me alone. What they
21 are saying is I want to have the information. I want to have
22 the privilege of saying no. I want to know what I am doing,
23 but don't abandon me; I need help.

24 DR. NERENSTONE: Mr. Dixon?

25 MR. DIXON: Yes, I want to go back to the

1 information point for a moment. One thing we have to keep in
2 mind is that there is another large government agency called
3 the SEC, which has very strict reporting requirements and,
4 while there is probably no one drug that is going to matter
5 or be material to a Merck or a Pfizer, for many of the small
6 companies, if they have a bad result in a Phase II trial
7 that is very definitely material reporting event which they
8 are forced by the SEC to disclose. Of course, many of us
9 read SEC stuff because we find a lot more there than waiting
10 for ASCO.

11 [Laughter]

12 DR. NERENSTONE: Dr. Lippman?

13 DR. LIPPMAN: I guess related point really
14 following up on Rick's point of the ASCO report and so on.
15 It seems as though the large major societies with tremendous
16 credibility, like ASCO and ACR, are actually taking a much
17 more active role in promoting these advances. It is a
18 different issue. I think part of it is that we want the
19 information to get out; it is important for congressional
20 information, to put more money into cancer research. It has
21 a lot of positive benefits but the downside is that although
22 an abstract may be selected for a high profile presentation
23 because it is extremely scientifically sound, very
24 provocative, and what-not, but it is still very early, not
25 really ready for prime time, and what happens is when that

1 comes out in a forum and ASCO has actually put their stamp
2 on it as something that they feel is very important, in that
3 context it will often get exaggerated in the press, and then
4 it leads to the false hope and all the issues we are talking
5 about. It is a change over the past several years, the more
6 active involvement of these large societies. So, if the
7 press want to exaggerate, or it maybe it makes sense that
8 they would exaggerate because it actually has the stamp from
9 these major societies. In other words, it is not just a
10 presentation of someone's abstract; it is actually that a
11 society is involved in that process.

12 I was just going to throw out a question. This is
13 something that came up to me when I was listening, that we
14 don't the want the exemptions to interfere with getting the
15 drugs through definitive trials to find out if they really
16 work and what the risk/benefit is, and if they meet that
17 then, obviously, you will get an FDA approval and get it out
18 to the public.

19 But one of the issues that comes up, and maybe I
20 missed it, is the issue of the issue of the randomized
21 trials where you may have, for instance, a 50-50 chance of
22 getting the drug that you really want to get as a patient,
23 and how would people view that because if you went on an
24 exemption you could get the drug and you know you would get
25 it, versus enrolling in a trial but when you are on the

1 trial you don't necessarily get that drug. I don't know if
2 there are any thoughts on that.

3 DR. NERENSTONE: Go ahead, please.

4 DR. LINDEN: Well, double-blind, placebo
5 controlled trials are always very problematic, particularly
6 when we think of them as the gold standard, but there are
7 some interesting ways to work around the dilemma you are
8 describing, and one of them is the use of cross-over designs
9 so that -- well, I will give you two instances of a cross-
10 over design that could make such a trial more attractive to
11 a person who would potentially enroll in that trial.

12 The first is that -- and this has been done in the
13 HIV AIDS arena -- there are two ways to do cross-over. One
14 is that when a person is in the control arm of the trial
15 experiences disease progression, that person in the control
16 arm can be unblinded and they can be given drug. So, they
17 are not consigned forever to nothing or to not having any
18 access to the study drug. So, that is one cross-over option.

19 Another cross-over option is the design of a trial
20 in which people on the study arm get drug and then they
21 cross over to a placebo arm and don't get drug for a period
22 of time, and those who were initially in the placebo arm,
23 after a certain period of time, cross over to the study arm
24 and get drug. So, the performance of both groups -- you see
25 a four-cell situation. The performance of both arms of the

1 trial can be observed with and without drug. And, there are
2 other ways to work that as well, but it creates some more
3 options that make trials more attractive to people who
4 otherwise wouldn't want to take the risk.

5 DR. LIPPMAN: I agree with that, those kinds of
6 designs though from a pure trialist, statistician or even
7 FDA point of view are often criticized, particularly if
8 survival is an endpoint, because it is almost impossible to
9 assess that unless you are looking at the effects of early
10 versus late therapy. So, it is an attractive aspect in one
11 sense but it limits your ability for some of the other
12 endpoints. And, I wasn't even just talking about placebo
13 control. I mean, we have seen randomized trials today, in
14 this couple day meeting, where everyone knew what they were
15 getting but you hope that someone would stick with that.

16 The only reason I bring this up is because it
17 seems as though the one thing everyone seems to agree on, at
18 least the FDA and the industry, is that the number one
19 priority is if there is a trial, then people, if they are
20 eligible, have to go on that trial. I am not sure that
21 patient advocates or patients see it that way if they have a
22 50-50 chance of getting the drug.

23 DR. NERENSTONE: Mr. Erwin?

24 MR. ERWIN: Mr. Dixon made my first point so I
25 will skip that, and the second point about cross-over, I

1 think that this is a very important issue that should be
2 addressed in parallel with the rest of this. I think, as you
3 pointed out, there is disagreement. An individual patient
4 will not like the possibility of being randomized to
5 standard of care, but from a policy standpoint or a
6 scientific standpoint, I am not sure there is a great answer
7 as to how to avoid that at this point.

8 DR. NERENSTONE: Dr. Pelusi?

9 DR. PELUSI: In part of that, one of the things
10 that I think we are all saying is that we want equal access
11 to quality care, and the one concern that I have, and I keep
12 hearing over and over again, is that we want access to drugs
13 that we think are very safe. I think at this meeting we saw
14 -- and at other meetings in the past -- that you may have a
15 Phase II study that on the outside appears to have some
16 great effective, to have a low toxicity profile, but when
17 the true review is done perhaps that is not all of the
18 information. So, what I think we need to keep in mind as
19 well is if we are going to look at access in terms of
20 compassionate use, single patient or group, is that are
21 these good studies, and I think that that mechanism needs to
22 be there as well, and I don't think that we can just say
23 everything should be opened up. I think that is something
24 that becomes very important as to who really looks at the
25 studies, who really gives this overall blessing, if you

1 will, that this is something that needs to be looked at for
2 compassionate use.

3 Just two other brief comments, it does show us
4 that we all have great responsibilities. It is not a
5 responsibility just of media, just the physicians and nurse
6 and industry, but it is all of together and that is what
7 makes it so complicated. But I think that we heard very
8 strongly today from all of the patients and patient advocate
9 groups that if we are going to have information out there it
10 needs to be the right information. It needs to be good
11 information and that there is a major educational piece that
12 must go forward that each of has to do in our own arenas.

13 Thirdly, to me, what was blatantly missing today
14 are the voices of our minority populations. As we all say,
15 the standard of care is going to be obtained by looking at
16 clinical trials, again, not only are we very low in patients
17 being accrued to clinical trials, but even more so in our
18 minority populations, which includes the elderly as well. I
19 really hope that as this discussion goes forward and we
20 begin to look at this we look at the issues of those voices
21 that may not be heard at this table. Thank you.

22 DR. NERENSTONE: Dr. Carpenter?

23 DR. CARPENTER: I just wanted to pick up on the
24 point of cross-over designs, particularly the cross-over
25 design with standard therapy. Cross-over with placebo in

1 early disease is a little different. But frequently the
2 basis for marketing may be an increase in survival, and if
3 you have a cross-over design in a Phase III trial against
4 standard care you will give up the ability of the trial to
5 detect a difference in survival. So, the very basis for
6 marketing a new drug and the very basis for understanding
7 the impact of the drug on the disease, which in the long-run
8 is what we all want to know, is compromised. So, there is a
9 tension there that needs to be resolved in order for this
10 process to be balanced because I think we want to make the
11 system as open as we can make it, but we don't want to make
12 it so open that we give up the very thing which we need the
13 most, which is which of the drugs that in the long-run are
14 really the most valuable for the people with that particular
15 cancer.

16 DR. NERENSTONE: Dr. Sugarman?

17 DR. SUGARMAN: I want to pick up on this point
18 about designs. There is a lot of confusion about the ethics
19 of competing research designs, but it crucial to
20 understanding the ethics of the whole process and,
21 unfortunately, it is hard word, it is even harder I think
22 than learning ethics sometimes -- big p values and little p
23 values and now you properly design research. Issues of
24 placebo needs to be separated from issues of randomized as
25 well as alternative design mechanisms. The world is

1 currently confused about placebos. Witness the recent
2 Declaration of Helsinki, which actually occurred in
3 Edinborough, not Helsinki, which confuses me geographically.

4 [Laughter]

5 But there is considerable therapeutic
6 misconception about the roles of placebos throughout. So,
7 that is one set of questions.

8 The question of randomized becomes very important
9 because what we have learned in the autologous bone marrow
10 transplantation in breast cancer is the example. It is a
11 very pertinent example about the use of innovation of a
12 powerful story about why it would be inappropriate to
13 randomized from the perspectives of people facing
14 devastating illness. Scientists and investigators were
15 convinced for a variety of reasons that this was going to be
16 a good idea. It made sense to some folks and not to others.

17 I think as this discussion moves forward you need
18 to get some of the design issues on the table. One of the
19 approaches I would hint towards, and that is all there is
20 going to be time for without stealing all the rest of the
21 time, is a notion of one way of understanding ethics of
22 randomized, a notion called clinical equipoise in which
23 there is uncertainty in the community about whether
24 treatment A versus treatment B or treatment A versus placebo
25 is appropriate, and if it is okay that is a starting place.

1 It is not the be-all and end-all. There are some
2 contraindications to randomized after that. That needs to be
3 understood. It might be worthwhile to consider playing that
4 notion of clinical equipoise out through the informed
5 consent process, through the public notification process so
6 that the potential research subject, the patients with this
7 who cannot be enrolled or could be enrolled can be in
8 equipoise to understand that uncertainty about the
9 scientific question, to realize the inherent biases to their
10 requests or their clinicians' request for treatment off or
11 on protocol. It is really when you are uncertain, you just
12 don't know and you are going to be fooled unless you randomly
13 assign. So, I would think -- it is hard; this is tough stuff
14 to communicate, but I think that would be helpful as a
15 public education effort.

16 DR. NERENSTONE: Mr. Dixon?

17 MR. DIXON: Mr. Erwin made my point.

18 [Laughter]

19 DR. NERENSTONE: Dr. Lippman?

20 DR. LIPPMAN: Yes, I would just like to underscore
21 that last point and hope that that could be used. I mean, if
22 you want to pick a couple of examples -- you know, you
23 showed elegant examples of different things but that would
24 be a very good example of where the community and the people
25 felt so strongly about uncontrolled data that if the

1 randomized study hadn't been done we would have had a self-
2 fulfilling prophecy and it is a very good example of where
3 when we abandon the normal way that we develop drugs -- you
4 know, they may not turn out. So, I think this is a good
5 example to bring up as we move forward.

6 DR. NERENSTONE: Dr. Linden?

7 DR. LINDEN: Into Dr. Sugarman's muddle, if I may,
8 of placebos and randomized and -- what was the third point?
9 -- placebo, randomized --

10 DR. SUGARMAN: And Helsinki.

11 DR. LINDEN: Yes, right, there is yet another
12 variable that complicates things, and that is the question
13 of surrogate markers and how impoverished we are at this
14 point with surrogate markers to make sense of trials as they
15 progress. It is an area that is in grave need of
16 advancement.

17 DR. NERENSTONE: Dr. Taylor?

18 DR. TAYLOR: One of the things he said was about
19 equipoise and I think it is one of the most different things
20 since we are dealing with a vulnerable population, and that
21 vulnerable population wants to get well, and understanding
22 equipoise is different when you are in medical school in
23 your third year. It is almost impossible when you are in a
24 position of a life and death situation. So, I think it is
25 really very different to do it and get the appropriate

1 informed consent. It is the right way to do it, but I think
2 it is different, and I think it is another reason why people
3 are always seeking the brand-new drug and not willing to
4 accept that the standard of care may be the best care and
5 the new drug may not be the best.

6 DR. NERENSTONE: Any further comments? Dr.
7 Lippman, last comment?

8 DR. LIPPMAN: These great ideas are coming at the
9 end of the two days, but the other great examples -- when
10 you start thinking of examples where we all assume that they
11 were better than the original -- the other great example to
12 use would be the lymphoma work. You know, if ten years ago
13 someone would have given CHOP -- it was absolutely accepted
14 to be inferior. There are editorials written about first
15 generation, second generation and all the other things and
16 then, of course, the definitive randomized trial shows that
17 CHOP is the standard. So, one could think of a lot of very
18 good examples where, when we did not follow this path, we
19 got burned.

20 DR. NERENSTONE: I would like to thank all the
21 participants for coming and the committee, and we will take
22 this up again in March.

23 DR. TEMPLETON-SOMERS: I would like to thank
24 everybody else for being patient with our ambitious agenda,
25 and mark your calendars for the March meeting, which is on

1 the 13th and 14th, exactly three months away.

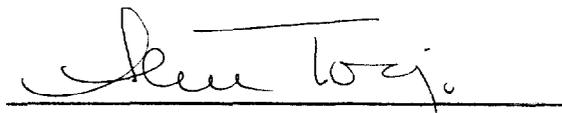
2 [Whereupon, at 5:05 p.m., the proceedings were
3 adjourned.]

4

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C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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