appeared because for the first time people worked in an environment where there was a high concentration in an enclosed space of processed materials, wool, hair, hides.

That generated and produced a new disease that was recognized by the medical community. That was wood sorter's disease, or rag picker's disease in Austria and in Germany.

And this is from William Greenfield, whom you heard briefly about, and I just point out this statement, that great swelling of the bronchial glands occurred, these being sometimes completely broken down by hemorrhage and transformed into blood clots; extensive cellulitis together with hemorrhagic effusion around the bronchial glands and in the mediastinum generally.

Serous pleural effusion, often in great amount, pretty equally in both pleura, usually unaccompanied by any signs of pleural inflammation, and in the lungs the changes are but slight.

So we've unfortunately had an opportunity to rediscover this disease with Sverdlovsk,b ut it was

well known to the physicians of the early or late 19th Century.

Slide off, please.

Now, there have been, as you've heard, very few cases in the U.S. There are some 18 reported cases, a few others throughout the world. Up until Sverdlovsk about 100 cases worldwide, and now with Sverdlovsk maybe 200 or so in humans that have been reported.

There have been several animal models that have been used to study this disease, but the non-human primate, particularly the Rhesus macaque, has been the model that has been used in the '50s and again more recently.

We've had an opportunity to study this because after the Gulf War began, we were asked to address a simple question: how to treat someone who had been exposed to an aerosol of anthrax spores?

And as a result of that, we generated some additional data which, together with the previous data in the non-human primate, gave us some more information about the pathology of this disease.

The next slide, please.

I hope you can see this. If not, I'll point out the highlights here. Is that a little out of focus?

PARTICIPANTS: Yeah.

DR. FRIEDLANDER: Good, good. And I'll just go over the highlights here.

Intrathoracic lymph nodes. There are two tables I'll show. These were compiled by Dr. Gary Zauchar, a veterinary pathologist at USAMRID, and they summarize the experience in the literature of the human disease and in the Rhesus monkey. This is all data at USAMRID, 25 animals, which includes the controls from the experiment I will describe, plus some others.

Intrathoracic lymph node involvement. Of the 72 cases he could find in the literature, that is to say the 41, 42 from Sverdlovsk, plus about 30 others, about 90 percent; in Sverdlovsk this was 100 percent.

In the Rhesus, about 80 percent of animals have involvement of the intrathoracic nodes. In the

mediastinum, various changes have been noted in about 80 percent; again, in the Sverdlovsk series 100 percent.

Here this is somewhat lower, about 40 percent.

If you look at primary pneumonia, 30 percent, and this does include as pointed out by Dr. Walker nonbacterial pneumonia, that is to say some hemorrhagic pneumonia without bacilli being present.

In the Rhesus it's about 16 percent.

In that regard, I should point out that there is some old data in the Rhesus macaques from the '60s that were infected with mites in the lung, and a characteristic lesion was described, not unsimilar perhaps in some cases to the arc welders. That is to say localization at the site of previous damage in the bronchial where that may be a source of entrance of the organism where it could persist.

In terms of the brain, the total CNS involvement, about 50 percent, and again in the Rhesus about 50 percent.

There are some differences in terms of

mesenteric lymph node involvement. Whether these are due to how careful the specimens are looked at, of course, is very difficult to tell.

And as was pointed out, there's one other point to mention here, and that is the survival time in the humans versus the various animal models.

In the Rhesus macaque, this is the average, about 4.8 days, five days post exposure at the time of death. That's about the same post onset of illness to death in the summary of all the human cases reported.

So there's a longer incubation period. There's a longer time to death in the human model than there is probably in the primate.

Now, that has to be couched particularly with Sverdlovsk, in my view, that we really don't know the details of these cases. We really do not know. There's been disinformation that's been given out before, as you're all well aware, and we don't know the specifics of the treatment of all the case as fairly quickly, as I understand it, after the diagnosis was made at least household contacts and

others received antibiotics.

So it's unclear whether the longer incubation period is, in fact, modified by individuals once this was known to the community going out either on their own or through the physicians and getting antibiotics.

Next slide, please.

In regard to the pathology, there's one point I'd like to make, and that's this question of the relationship between the duration of the illness and the pathologic findings, and if you just concentrate on the Rhesus monkeys here, these are the total number of animals. They're small numbers, but there's a suggestion.

Here's the mean survival time, from three days out to seven to eight days. As the animal survives longer, the incidence of mediastinal disease increases -- there's only one animal out here -- as you might expect.

That is to say if the disease is first in the node, the longer the animal lives, the more likely it is for it to spread to the mediastinum and for you

to see the pathological changes at autopsy.

And, similarly, if you look at these six animals that died on day three, CNS involvement was 17 percent. As you go to day four, five, six, seven, the incidence of CNS involvement again goes up, suggesting the longer the animal survives, the more inflammatory cells you see and the more extensively disease is, approaching more that of the human.

Next, please.

Now, this shows some examples of the characteristic finding to be anticipated in this disease, and that is the widened mediastinum.

Next slide, please.

Relatively clear lungs.

This is another case, again, a widened mediastinum with pleural effusion.

Next.

This is an over penetrated chest X-ray of a Rhesus macaque. Here's a normal animal, and here's the widening of the mediastinum that, again, is really quite evident.

Next, please. Could you -- that's okay.

I'm a little disoriented here.

This is the trachea. The head is here. Phrenic nerves. That's the business end of this disease, very analogous to what you saw Dr. Walker present in the human cases, that hemorrhagic enlarged node.

It's difficult to tell about this glistening edema of the mediastinum. Unless it's hemorrhagic, it's not something that one would easily pick up.

Also notice the pink lungs. So this is the disease we're really talking about. It's really mediastinitis.

Next, please.

This is the same brain that must be traveling around the world now very frequently from a case in Sverdlovsk.

(Laughter.)

DR. FRIEDLANDER: Next, please.

This is one of the Rhesus monkeys, entirely comparable lesions.

Next, please.

Now, as soon as the Gulf War, as I said, started -- you can take that slide off -- we were asked to design studies to address this question. There had been prior studies in the literature by a group in England, as well as the U.S., that attempted to address this issue in the Rhesus monkey model, and they used post exposure antibiotic treatment for varying periods of time, for five days and ten days, and what they discovered is that the animals survived while they were on treatment, but once the treatment stopped, the animals died of anthrax.

There was one experiment done with a 20 day course of antibiotics. It was complicated by various other infections that the animals had. Again, about a third of the animals died, but they were very small numbers.

What they did show was that if you gave antibiotics a vaccine, you did protect the animals post exposure.

Now, a rational treatment of inhalational anthrax has to take into account a couple of obvious facts that I think most of you are now well aware of,

and that is that the spore, as we know, can survive for decades and probably hundreds of years in the environment, but it also can survive in the host for extended periods of time, and that creates a very difficult therapeutic situation because while it can survive, once you discontinue antibiotics, the spore may then germinate.

And this was really established by Barnes in 1947, and that's what the next slide shows. I should point out that in the first paper by Abraham, Chain and Florey on penicillin in 1941, one of the organisms, in fact, they looked at was Bacillus anthracis, and shortly after the first human cases in '44, I believe, were treated cutaneous with penicillin.

Barnes studied this in the mouse and pointed out that one of the main factors in the therapy of inhalational anthrax is the persistence of spores in the tissues and their germination after the blood penicillin level has fallen, and that remains the dilemma that we have."

Next slide.

And this is another issue that also remains an unknown. Unfortunately we have lots of unknowns, no assurity. That is, the conditions which govern the germination of anthrax spores in vivo remain completely obscure.

I should say they're almost completely obscure in vitro. People are just now beginning to look at the germination genes in Bacillus anthracis, and an operant that's involved in germination, at least one set of genes involved in germination has recently been discovered. But we don't know what causes the spore to germinate, why it sits around, and why it may at day 20 or 30 appear to germinate.

Next, please.

Now, this idea was given further empirical support from the data of Henderson, and what Henderson showed was that in the Rhesus monkey, you could recover spores. These were done in treated and vaccinated animals, but you could recover viable spores for extended periods of time.

And what I've done here is basically plot. This is from Henderson's data. He had data showing

about 15 percent of the inoculum surviving at 42 days, about two percent at 50 days, and there were traces even at 100 days.

Excuse me. I just want to get water.

And what I've done is show this graphically here. If you start with ten LD-50s, you're below an LD-50 at about a month or so, but if you're up at 100 or 1,000 LD-50s, even out at two and a half months or so, you're still above an LD-50.

Now, there are a lot of assumptions based on this data, but there is support for it both from Henderson's work and as I'll show you from our work that animals can die after an extended period of treatment when you stop the antibiotics.

So I wouldn't put too much credence in the -- there are no error bars here. There are few animals. Nevertheless, conceptually the idea, I think, is a valid one.

Next, please.

So this basically summarizes the point. The spore may persist in a viable but ungerminated state for extended periods of time, and that

antibiotics do not act on the spore. They act only after it begins to germinate.

So we sought to determine, as I said, whether a more prolonged course of therapy could be effective alone or in conjunction with vaccination.

Dr. Meyerhoff asked me to describe briefly some of the effort and urgency that went into performing this experiment. Given the nature of the events that occurred during the Gulf War, I can tell you that we were truly on a wartime footing working seven days a week for months to try to get this experiment done as quickly and as well as we could because an answer needed to be given.

Next slide, please.

This shows the chronology of the events. Iraq invaded Kuwait on the 2nd of August. The first challenge in two Rhesus monkeys took place on the 29th of August. During that period of time we had to develop an aerosol model for the monkey. We had not done that at USAMRID in modern times.

We had to get 68 monkeys from around the country, in addition to writing animal protocols and

getting them approved. That was a lot easier actually than getting the monkeys.

And during this period of time, we also performed a preliminary pharmacological study because we had very limited data, and that took place about the same time.

So within about two weeks we demonstrated that we could aerosolize spores with a lethal dose in two monkeys and did preliminary pharmacology in six monkeys, two each with two antibiotics, and the experiment began on the 13th of September.

Next slide.

There were more than 60 people that were involved in the design and the implementation of the experiments. There were 68 monkeys used, eight in the preliminary experiments and 60 in the post exposure prophylaxis experiment.

There were 3,780 courses of anesthesia given to these monkeys; 1,550 quantitative blood cultures; parenteral medications, 720; oral gastric medications, 1,920.

One animal died from aspiration pneumonia,

and one animal died from unknown causes. It really was an effort for the veterinary support and the animal handlers here, I think, to accomplish this so quickly and without significant side effects really to the animals.

Next, please.

This is the experimental design. It was quite simple. On day zero the animals were challenged with eight LD-50s, lethal dose 50s, by aerosol. Day one, treatment was begun with antibiotic alone, vaccination alone, or the combination in one group. This is actually day 31. They got 30 days of antibiotics, and then it was discontinued.

They were rechallenged about three and a half months later with a higher dose, 50 LD-50s by aerosol.

Next.

There were ten controls. They got saline. They were basically a control for the penicillin group. They got saline intramuscularly every 12 hours beginning one day after exposure until the time of death.

The penicillin group, there were ten animals treated with penicillin G, IM every 12 hours for 30 days. This dose -- I'll mention that in a moment.

Ciprofloxacin, there were ten animals treated at a dose of 125 milligrams every 12 hours, again, for 30 days.

Doxycycline, the same regimen, except 30 milligrams by oral gastric tube every 12 hours for 30 days.

Doxycycline, the same regimen, but in addition, they got a half an mL of the AVA vaccine on days one and 15 following aerosol exposure.

There was another group that just received post exposure vaccine on days one and 15 following aerosol exposure if they survived. As a control they received water by oral gastric tube every 12 hours. The oral gastric medications required anesthesia.

On the basis of the initial pharmacology, which was based -- there was no literature that we could find about tetracycline and penicillin in the Rhesus. There was a little bit of data on

ciprofloxacin. We based the dosage on body surface area and modified it slightly based upon two animals per group.

So that we upped the dose of penicillin a little bit, of doxycycline, and we gave loading doses of ciprofloxacin. The first dose was double the dose, and this was based just upon the initial two animals.

Next, please.

I just point out a couple of things here. There were daily blood cultures from the untreated controls in the vaccination groups until death or for 14 days. In the antibiotic treated groups, the blood was cultured every other day until 80 percent of the controls died, and then twice weekly until day 30.

When the antibiotics were discontinued, the were cultured every other day until day 60, and then once a week until rechallenge.

ELISAs were done. All of the animals were observed at least twice daily until death or euthanasia, and a diagnosis was confirmed in all of the animals that died by isolation of Bacillus anthracis from the blood, and in all the deaths in

which the cultures were negative, cultures were obtained at autopsy of the blood, spleen, liver, lung, intrathoracic nodes, and brain.

Next, please.

The antibiotic sensitivity test that we performed with this strain showed that in Mueller-Hinton broth the MIC was 0.08 micrograms for penicillin. For ciprofloxacin, this strain, 0.08, and the values for doxycycline are given here.

The NBC was equivalent to the MIC for ciprofloxacin.

The serum levels were determined by bioassay. Peak levels were determined at one hour pos dose for cipro and two hours for penicillin and doxycycline after doses on day five through 30, five, nine, 20 and 30.

The trough levels were determined 12 hours after a dose.

Next, please.

In the central panel, which you can make out in B here, this is a log scale of the geometric mean serum levels. I mentioned that, I think in the

read-ahead package. As we discovered, this is presented slightly differently as arithmetic means that you may hear about.

But the MIC was 0.8 about across here, and these are the geometric means of the trough on day three, five, nine, and 20, and as you can see, they're above the MIC. The trough is for all -- throughout the period of the study.

These are the peak levels, the means, and then they are at least tenfold higher than the MIC and MBC throughout the course of the experiment.

Next slide, please.

And that's just reiterated here. The actual values, geometric mean, peak levels were between 0.98 to 1.69, while the trough levels were between 0.12 to 0.19 micrograms per mL, and the MIC and MBC for this strain was 0.08.

Next, please.

This shows some of the findings in these animals. This is the control group. Nine of the ten control animals died, with the mean time to death of 5.6 days. This issue that animals are not ill until

time of death is fallacious in the Rhesus macaque. These animals are ill. They're ill for anyplace from one to four days before death.

There's decreased spontaneous activity. They go off their feed. They're weak. They're anorexic, not unlike the situation in humans.

Bacteremia occurs for a mean of 1.8 days before death with low to fairly high levels, ten to the one to ten to the fifth colony forming units per mL.

Terminal bacteremias are usually quite high. There was one animal with a low terminal bacteremia of 200 organisms per mL that had meningitis with two times ten to the seventh CFUs per gram of brain tissue. Five of nine of these animals had gross findings of mediastinitis and intrathoracic, hemorrhagic lymphadenitis, and in five of nine meningitis was present, and it was hemorrhagic in three of the cases.

One animal survived, had persistently negative blood cultures.

Next.

In most of the animals the organisms were all over the place. This is an easy diagnosis to make.

In a few animals, the organisms were more difficult to find, and I just point this out. This is immuno-histochemistry by EM with an antibody to a polysaccharide in the cell wall that clearly outlines degraded organisms in a macrophage.

Next.

This is just a higher magnification showing degraded bacilli that are coated with this antibody, with gold particles.

Next.

Now, these are the results of the experiment. The control, as I mentioned, nine out of ten animals died. With vaccine alone post exposure, eight out of ten died. With penicillin, three out of ten animals died.

Now, this is at three and a half months. this is 30 days of treatment, off drug for three to three and a half months. This is the long term survival.

None of the animals died while on antibiotics from anthrax. They all died subsequent to discontinuing taking the antibiotic.

In the ciprofloxacin group, one out of nine animals died after going off ciprofloxacin. I'll talk about these animals in a little more detail subsequently, but there was one animal that died five days after exposure from an aspiration pneumonia, had no evidence of anthrax on autopsy, and this animal was excluded from analysis.

As I'll mention, there's a second animal that died 73 days after stopping ciprofloxacin. This was due to urethral obstruction, and there was no evidence of anthrax at autopsy, and this animal was included in our analysis as a survivor.

For doxycycline, again, none of the animals died while on treatment. One animal died when the doxycycline was discontinued.

In the group of doxycycline plus vaccine, none of the animals died due to anthrax. There was one animal that died six days after discontinuing the doxycycline, but had no evidence of anthrax on

autopsy. The cause of death in that animal is unknown. There was some mild myocardial degeneration, mild, but we don't know why that animal died, but the animal was excluded from statistical analysis because it had only been off antibiotics for six days.

So there was a statistically significant increase in survival in all the groups that had received any antibiotic.

Next slide, please.

So the conclusions from this part of the study were that vaccination alone begun after exposure to anthrax spores did not protect animals; that all of the antibiotics, including ciprofloxacin, provided complete protection when given after the aerosol exposure to spores, as long as the animals remained on treatment.

An extended 30 day treatment period with either penicillin, ciprofloxacin or doxycycline alone provided significant long term protection upon discontinuance of therapy, with from 70 to 90 percent -- that's 89 percent for the ciprofloxacin group -- of the animals surviving.

That post exposure vaccination when combined with doxycycline protected all of the animals. This difference was not statistically significant because most of the animals survived with just antibiotic.

Now, the animals that survived exposure were examined for evidence of an immune response. None of the animals treated with just antibiotic had any evidence that they had seen anthrax by the antibody assay that we used, which was an antibody to protective antigen. That is, they behaved as if the infection had been aborted, and they did not generate an immune response.

The only animals that generated an immune response was the group that received doxycycline plus vaccine, and so it appeared, as I said, that the antibiotics totally suppressed the infection.

The next slide, please.

We looked at the resistance of the survivors at three to three and a half months after discontinuance of the antibiotics, and they basically confirmed what the antibody data had predicted,

namely, that the animals that were treated, whether penicillin, ciprofloxacin, or doxycycline alone succumb to rechallenge. They were not immune. Only the doxycycline plus vaccine group survived, and these differences, again, are statistically significant.

Next slide, please.

The overall results are shown graphically. I like to show this slide because it's one slide that has all the data. It's six months of work with 60 people. So for a short lecture, I just show this.

This shows the control group. Here's the time of exposure. The vaccine alone group, the animals die. Antibiotic treatment for 30 days, the animals all survive.

I want to point out this animal in the ciprofloxacin group. This ciprofloxacin group is the open triangles, and we'll focus on that. Just first these are the three penicillin animals, the closed triangles, day nine, 12, and 20. Following discontinuance of the drug three animals died. Again, on rechallenge these animals die.

The doxycycline alone group, one animal

dies at 28 days after discontinuing the antibiotics. That's 58 days after the challenge. Again, these animals die on rechallenge.

And now the ciprofloxacin group. This animal was the animal that died from aspiration pneumonia. There was one animal that died on day six, I believe. I just want to make sure I got -- this animal died of inhalational anthrax with hemorrhagic necrotic lymphadenitis, intrathoracic nodes and mediastinitis.

This animal died on day 73, and that is 103 days after exposure. The animal developed urinary obstruction. The urine culture showed non-hemolytic staphylococcus. The blood culture was negative. There were attempts to relieve the obstruction, but the animal was euthanized five days later.

At autopsy there was no evidence of anthrax. I wanted to clarify a report in which this animal's pathologic tissues were reexamined just within the last few weeks. There was, again, no evidence of anthrax in this animal. There were urethral concretions, rubbery concretions which have

been described in male primates that was the cause of the obstruction at the trigone of the bladder and in the urethra.

In summary then -- next slide -- post exposure antibiotics, including ciprofloxacin, which protect against an aerosol challenge with spores appear to prevent actual infection in the development of an effective immune response. So that while animals survive with an extended course of treatment, they remain non-immune and susceptible to rechallenge.

Post exposure vaccination, when combined with antibiotics, does protect animal both against -- with the antibiotics -- against the initial aerosol challenge and leads to the development of an effective immune response so that these animals are resistant to rechallenge.

And, therefore, the most effective post exposure treatment of experimental inhalational anthrax consists of suppressive antibiotic therapy combined with vaccination.

Thank you.

CHAIRMAN RELLER: Thank you, Colonel

Friedlander.

Before a 15 minute break we'll take any questions for Dr. Friedlander from the panel. Yes, Dr. Chesney.

DR. CHESNEY: How old were the animals?

DR. FRIEDLANDER: The animals were of varying age. My -- I know more the weights than the age, and I'd have to look it up. I think were from four to about 12 kilograms. I have the paper here. I can get that for you. They were of varying ages.

DR. SOPER: What about the use of passive immunity immediately along with active immunization?

DR. FRIEDLANDER: Good idea.

DR. SOPER: And the reason was you're just now characterizing the toxin.

DR. FRIEDLANDER: Well, we don't have a supply of antiserum. As you know, before the introduction of antibiotics antiserum was used as it was for most infectious diseases. There were never any control trials done, but there's good evidence in animals, as well as the anecdotal evidence of physicians that it was effective in cutaneous disease,

and there's some evidence in the Rhesus model, in fact, that it's effective against inhalational anthrax.

So I think it's a possible adjunct therapy in the future.

CHAIRMAN RELLER: Yes.

DR. DEITCHMAN: Just to follow that up, what would be the duration of passive immunity, and would it get you much further than up a long course of anti-infectives?

DR. FRIEDLANDER: That's a good question. I don't know the answer to that.

In the Rhesus, it appeared as if just a couple of doses of antibiotic the animals were carried out for some 40 days, I think, and there was significant survival.

It depends. I mean, what you're talking about here is probably passive-active immunization, and that could get tricky. You've got to have enough coverage, but you're probably got to have some development of active immunity, is my guess.

CHAIRMAN RELLER: Thank you, Colonel

Friedlander.

Yes, Dr. Chikami.

DR. CHIKAMI: I have a quick question. The data you showed from the early Henderson studies show that there is a fall-off of retained spores within the lung. Is it known what the mechanism of that spore clearance is?

DR. FRIEDLANDER: Nobody has done anything more on that other than the conjectural data that was generated by Henderson and Barnes. I mean, so I really don't have any data.

I mean, as you know, only a certain percentage of the inhaled dose is actually retained, 15 percent or so, and, again, this is from Ross' studies showing sort of degenerated macrophages going up the mucosiliary tree. Presumably if they can get to a bronchus, they'll be expelled, not unlike other particles.

I mean, there's no evidence to think that they would be handled that differently, but there's no data on that.

DR. CHIKAMI: And is the inevitable

interaction between a macrophage and the spore that the spore will germinate into the vegetative?

DR. FRIEDLANDER: No, not at all. I think there's evidence that most of the spores are probably killed, but, I mean, if you look at Ross', it's hard to come up with numbers, but I mean, an inhaled dose is -- it's a good dose, but a lot of things have to happen for one to get to a node. When it's one or nine, I don't think anybody has a clear feeling.

In vitro spores can be killed by macrophages.

CHAIRMAN RELLER: Thank you.

Let's convene promptly at noon. Then we'll hear the FDA presentation and lunch we'll aim for at 12:30.

(Whereupon, the foregoing matter went off the record at 11:43 a.m. and went back on the record at 12:02 p.m.)

CHAIRMAN RELLER: Dr. Gary Chikami, who is the Director of the Division of Anti-Infective Drug Products will initiate the FDA's presentation to be followed by Dr. Andrea Meyerhoff, who was the medical

reviewer from the Division of Special Pathogen Immunologic Products for this application.

Dr. Chikami.

DR. CHIKAMI: Thank you, Dr. Reller.

I'm also speaking in my sort of role as the coordinator within ODE-4, the Office of Drug Evaluation-4, in dealing with issues related to the response within CDER to issues related to counterterrorism activities and the response to these sorts of issues.

I'm just going to provide an overall sort of introduction to Dr. Meyerhoff's presentation, which will really do the heavy lifting in terms of the FDA's perspective on these issues. I think the agency, as you've heard from Dr. Murphy's remarks at the beginning of the session this morning, recognized that there's a need for an adequate medical response to protect or treat individuals who might be exposed to lethal or permanently disabling toxic substances.

And so I think that in that regard there are some special aspects of the particular situation that we have under discussion today.

And you can go to the next slide.

This represents a particular group of products which are intended or may be shown to prevent the toxicity of a legal biologic agent that could be involved in emergency setting, for example, an act of terrorism or in military situations.

I think a second characteristic as we looked at this particular situation is that the product may provide sort of the meaningful therapeutic benefits over existing therapies. As you'll hear, there are other products, other products that have been studied in inhalational anthrax as you've heard, but I think there is a perceived need for alternatives to treat individuals who are exposed to these lethal biologic agents; in addition, alternatives that may address the issue of potential antimicrobial resistance of a biologic agent.

As Dr. Murphy pointed out earlier this morning, this is a situation where traditional efficacy studies in humans may not be feasible either because it's unethical to expose volunteers to these agents or, in the case of certain diseases because of

their unique epidemiology, that is, their rarity, field trials may not be doable or feasible.

As we've thought about this situation, we've thought what is the body of evidence that could be assembled and that are available to address the issue of efficacy in this situation, and I think parenthetically this is a situation where we're talking about marketed products which already have an established safety track record so that the issue of safety, I think, is not really a big issue in this situation.

Next slide.

So what are the available types of evidence that could be assembled? And you've actually heard some speakers this morning who have actually gone over in great detail some of these aspects, but I wanted to sort of briefly summarize them and put them into a form that tried to organize them into sort of the logical progression that we've used in our own thinking within the agency.

That is, is there an understanding of the pathophysiology of the disease under question? Is

there an understanding of the mechanism of action of the drug and its prevention of the pathologic process? Is there a demonstration of a protective effect in an animal species with a response that is protective, predictive for humans? That is, is the disease in the animal model relevant to the human condition?

And in this case we've heard a detailed description of a non-human primate model for inhalational anthrax, and moreover, the benefit or the endpoint that's demonstrated in the model is clearly related to the desired benefit in humans, that is, survival.

And finally, do we have information on the pharmacokinetics and pharmacodynamics in animals and humans sufficient to allow us to select what we think will be an effective dose?

Next slide.

What I've tried to do here is to put this in sort of a flow chart. We have sort of -- in trying to come to a conclusion in overall efficacy and safety in this situation, I think as Bayer described earlier there is a substantial clinical experience with safety

for this product, given its long history of marketing and its extensive use, clinical use.

In this side of the graph is where we come to the body of evidence that might be available to support a conclusion that in this particular situation there is evidence of effectiveness starting with in vitro activity of the product, data from a relevant animal model, and then linking that information to our understanding of human pharmacokinetics and the animal pharmacokinetics to a prediction of clinical effectiveness.

With that I'll close and then have Dr. Meyerhoff actually present the body of the FDA presentation.

DR. MEYERHOFF: Thank you.

As mentioned, I'm going to be presenting the perspective of the FDA Scientific Review Team on this application. I'm going to touch on a number of areas that have already been discussed in considerable detail this morning, but I'm going to focus on aspects that are particularly pertinent to the regulatory review.

Next slide, please.

Firstly, I'd like to go over certain aspects of inhalational anthrax as a disease and then look at drugs to treat this, focusing on their regulatory status; made a few points about the microbiology of the anthracis; and then turn and look at what we know about the pharmacology of ciprofloxacin in both the species use and the animal model, the macaque and the human.

Lastly, I'd like to look at a number of studies of post exposure prophylaxis for this disease, starting with some older work that provides for us something of a background as we proceed to a discussion of the study under review, that is, the work presented by Dr. Friedlander.

Next slide.

As you've heard, anthrax particularly in its cutaneous form is a disease that's been known since antiquity. The inhalational form of this illness is a relatively new clinical phenomenon. It was only described in the mid-19th Century in the British textile industry.

The common usage names of this disease, wool sorters or rag pickers, attest to its industrial or occupational relationship.

It's very rare in this country. Since 1900, there have been on the order of about 20 cases total.

As you've heard in considerable detail, the organs affected and the kinds of pathology that result include a hemorrhagic mediastinitis with subsequent involvement of various organs of the reticuloendothelial system, the central nervous system, and in many patients the development of a sepsis syndrome.

Next slide.

Inhalational anthrax is the clinical entity thought most likely to result from the intentional use of aerosolized spores of B. anthracis. The mortality ranges between 80 and 100 percent of those with clinically recognizable disease even with the administration of appropriate therapy.

Historically penicillins and/or tetracyclines have been the drugs of choice. There

are some recent reports of bioengineered strains of this organism that have been penicillin and/or tetracycline resistant.

Next slide.

When we look at the status of agents approved for use here in the U.S., there is no drug approved for the prophylaxis of inhalational anthrax. There are drugs of the penicillin and tetracycline classes that do have indications for the treatment of clinical disease due to B. anthracis.

I think it's noteworthy to point out that any program for large scale use of an agent in either a civilian or a military population requires an approved NDA indication or an IND application with the FDA. This is in contrast with the practice of medicine, which FDA does not regulate and has no jurisdiction over the choices an individual physician makes to treat an individual patient under his or her care.

Next slide.

As you've heard earlier, cipro was first approved for use in the U.S. in 1987, and that was the

oral tablet form. There are currently 17 approved indications for this drug, and these include lower respiratory tract, complicated interabdominal and bone and joint infections, pertinent because either the site or the duration of treatment has some relevance to the indication we're discussing today.

Cipro is also approved for use in another infection of the reticuloendothelial system, and that is typhoid fever.

Use data in the U.S. suggests that the drug has been used by upwards of 100 million patients, and as we heard earlier from Bayer data, probably about 250 million worldwide have used the drug.

Next slide, please.

The approved doses of the oral form range between 100 and 750 milligrams of cipro, usually dosed at a 12 hour interval. The proposed regimen for anthrax prophylaxis for adults is 500 milligrams every 12 hours; for children, ten to 15 milligrams per kilo, same interval.

The duration of drug administration proposed is 60 days.

Next slide.

B. anthracis, as you have heard, is a spore forming, Gram positive rod. It germinates into the vegetative of pathologic state under certain environmental conditions.

The vegetative state is conferred virulence by both its capsule and the production of certain toxic factors, protective antigen, edema factor, and lethal factor.

Generally this organism in its vegetative state is susceptible to both penicillin and tetracycline. Naturally occurring isolates, however, do exhibit about three percent of the time penicillin resistance.

As I've mentioned earlier, there has been some recent reports of resistant strains, strains that are resistant to these two traditionally active agents.

Next slide.

This application included information on antimicrobial susceptibility testing in two series of B. anthracis isolates. The total number of isolates

was upwards of 90. I'm presenting data here from the larger series of 70 strains because it is representative of the entire population.

These are a mixture of clinical and laboratory isolates. They come from geographically diverse sources, from animal and human patients.

I think inspection of this table gives us a feel for the potency and susceptibility for ciprofloxacin in comparison to these other traditionally active agents.

As you can see looking at the MIC-90 values, the MIC-90 for these 90-odd strains for ciprofloxacin is just one dilution less, and that is .06 micrograms per mL.

I'm going to turn now to a discussion of cipro pharmacology. We are going to look at some data expressing serum concentrations first in the macaque, and this is data taken from the animals studied in the experiment described by Dr. Friedlander, and then we'll look at some data from human populations as well.

Next slide.

As you heard earlier, the work conducted by Dr. Friedlander's group included several cohorts of ten macaques each that received various antimicrobials. These data are from the ciprofloxacin receiving cohort that were exposed to aerosolized spores and then administered ciprofloxacin for 30 days.

These peak concentrations were taken at various points after steady state had been reached and show that peak levels ranged somewhere between 1.5 and two micrograms per mL. The Y axis here is a log scale of cipro concentration. The X axis, the actual days at which the sampling took place.

The pink line across the bottom is the MIC-90 for B. anthracis, and that's .06 here. That is for the series of strains submitted in this application. This is not from the strains described by Dr. Friedlander which has a slightly higher MIC of .08.

Next slide, please.

This slide presents data on trough concentrations in the same animals in a very similar

fashion. Again, log scales, cipro concentration on the Y axis, various sampling points after steady state has been reached.

The mean trough concentrations are roughly ten percent of the peak ranging between .15 and .2 micrograms per mL. The pink line, again, the MIC-90 of the organism.

Next slide, please.

This table presents pharmacokinetic data from three populations of interest following the oral administration of ciprofloxacin and the achievement of steady state.

The first population is the monkeys that were studied in the model of inhalational anthrax that we have been hearing about this morning.

The second population is human adults who have received a regimen of ciprofloxacin that is the one in the proposed label for post exposure prophylaxis of anthrax.

Similarly, the third population is human pediatric data that's from cystic fibrosis patients also receiving a dose that is in the proposed label 15

milligrams per kilo.

One thing I would point out is that the monkeys studied in the experimental model received a loading dose. Their first dose was twice the repeat dose they subsequently received. So 250 milligrams followed once, followed then by 125 milligrams every 12 hours for 30 days.

Inspection of the C-maxes shows that these are reasonably close, but note that the human populations without receiving the loading dose actually achieve higher peaks than the macaque. For the two populations for which we do have trough data, the monkey and the human, these are quite comparable.

Next slide.

This is a graphic presentation of those same data showing only the peaks. A very similar structure to the slides I've been showing earlier. the Y axis is the log scale of cipro concentration. Along the X we just have the individual populations.

Visual inspection shows that these are quite comparable levels, and again, we have the MIC-90 at the bottom.

This is a graphic presentation of the trough data for the two populations for which those data are available.

In a number of these slides I have been showing data about drug exposure compared with what we have seen of drug susceptibility in the in vitro testing submitted in this package.

These are not formal models of pharmacokinetic/pharmacodynamic testing. Those don't exist for ciprofloxacin with B. anthracis. But I think if we give a little bit of thought to what we know about fluoroquinolones and what we're seeing about this organism and about this drug, we can develop an idea of what drug exposure is relative to organism susceptibility.

Fluoroquinolones as a class exhibit concentration dependent kill rather than time dependent killing.

A few different parameters have been looked at, and I think that Andy Verderame mentioned these in some detail when he started talking about AUC to MIC ratios and C-max to MIC ratios as a way of

looking at a model that might predict clinical outcome.

We only have C-max data here. So that's what I'm going to talk about.

Some early work in Gram positive systems suggest that a ratio of C-max to MIC values that reaches or exceeds ten is a desirable range.

When we look at the data for ciprofloxacin peak levels compared to the MIC-90s for B. anthracis, we see that in the macaque the cipro peak is approximately 33 times the MIC-90 for B. anthracis. In the human the peak is about 50 times the MIC-90. This is using the value of .06.

If we use the value of .08, which was the MIC for the organisms studied in Dr. Friedlander's model, the ratio for humans is about 37 times the MIC.

Next slide, please.

I want to turn now and look at some early work in inhalational anthrax, specifically at post exposure animal models, but before I do that, I think it's helpful to look back at two early theories of pathogenesis of this disease.

Theory number one is what I'm calling the persistent spore theory. Following the inhalation of aerosolized spores and their deposition on the pulmonary epithelium, it was thought that pulmonary macrophages would phagocytose these spores, convey them through the mediastinal lymph nodes, and somewhere in that process the spores would germinate to the vegetative state, elaborate toxin, and start to cause the pathologic changes that we ultimately associate with clinical disease.

Theory number two was one of acute bacterial infection, and that suggested germination at a much earlier stage in the course of exposure to B. anthracis spores which was thought to gain a portal of entry into the deeper pulmonary tissues by an erosion of the bronchial mucosa.

Once in the pulmonary parenchyma, it was thought that spores would rapidly germinate, elaborate toxin, and produce their early pathology in the lung tissue itself.

Next slide.

Work undertaken by Henderson and

colleagues in the U.K. in the 1950s attempted to address these two divergent theories of pathogenesis by administering an antimicrobial, penicillin, following exposure of macaques to aerosolized spores of B. anthracis.

Their hypothesis was that if the persistent spore theory were the operative one, animals would only be protected from morbidity and mortality for as long as they received the antimicrobial.

Henderson's group performed a controlled experiment where following exposure, macaques received either five, ten or 20 days or nothing of penicillin.

If we look at the survival curves, which we will in a minute, of these four cohorts, we can see that they all seem to have the same slope as the control animals, that is, there's a precipitous drop in survival.

And perhaps the one conclusion we can draw from the administration of these relatively short courses of penicillin is that there main effect is to only delay death rather than prevent it.

Next slide, please.

These are the four survival curves of the four cohorts studied by Henderson's group. I'd just point out that both of these Y axes are the numbers of survivors. The X axis is the number of days following exposure.

The left-most and vertical-most survival curve is the control animals. None of them survived beyond eight days, but I think if we just inspect the curves for Groups A, B, and C, there is a parallel quality to them. Animals die quite quickly, but we can also see that the time of death is delayed somewhat proportionally to the duration of antimicrobial administration.

Next slide.

Another concept that was explored by Henderson's group has been discussed in some detail this morning. I'd just like to present it in a slightly different form here for the purposes of the discussion we're going to develop.

Looking at a number of the exposed macaques that were sacrificed at certain points

following exposure, I think there were 50 or so animals that were studied in this fashion. This group demonstrated that the proportion of retained spores in the lung fell over time. As we got out to periods 75 and 100 days following exposure, the percent of the original retained load was becoming smaller and smaller.

Next slide.

This concept was looked at from a slightly different perspective by Joan Ross, who published her work in 1957. Using a guinea pig model of inhalational anthrax, she noted that the number of spores that were reaching the regional lymph nodes in the mediastinum were markedly less than the number that were deposited on the pulmonary epithelium.

She developed a differential staining technique which permitted her to distinguish various stages of spore development and the vegetative state.

Doing a number of morphologic studies, she proposed a number of different modes of spore exit from the lung. One was the theory of pathogenesis that we have seen being tested and looking more and

more like the operative theory, and that is the phagocytosed spore being transported to the regional lymph node by the pulmonary macrophage.

She also noted phagocytosed spores that passed into bronchials and were presumably cleared from the lung via the airways, perhaps coughed up.

Lastly, she described spore ghosts that were halted in their development inside of the phagocytic cell and proposed that some proportion of spores are actually destroyed by the phagocyte.

Next slide.

I'm now going to move on to a discussion of our analysis of the work done by Dr. Friedlander and presented in great detail by him earlier. I just want to review a couple of salient points to help sort of follow through this discussion.

If you will remember, there were six groups of ten animals each, all of which were exposed to loads of aerosolized spores. Four of these groups received 30 days of antimicrobial following exposure. These groups received either ciprofloxacin, doxycycline, penicillin, or doxycycline plus vaccine.

There were two additional groups, one of which received vaccine only, the other which received control, saline.

We're going to discuss these results using two different analyses. Firstly, we'll look at survival following the aerosol challenge for the period ranging from day zero to 120.

As you heard Dr. Friedlander describe, there was a second challenge phase to this experiment that started around day 130, and I'm separating out and talking only about the period up to day 120 at this point.

We'll also look at mortality rates in two different populations at two different points in the study, and I will clarify the details of those as we get to them.

Okay. Next slide.

This is a simplified survival curve based on the one published by Dr. Friedlander's group in the 1993 publication included in your briefing package. It shows the survival curves for both the control and cipro animals. Survival is presented as proportional

survival on the Y axis and days post exposure on the X axis.

There are two heavy vertical lines on this slide depicting important points in this study. One is day 30, the cessation of antimicrobial administration. The other is day 90, which was the prospectively defined efficacy endpoint or what might also be called the test of cure time point.

I think from inspection we can see that there are two different shapes to the survival curves here. The control animals look very much like the control animals in the Henderson experiment, steep, steep drop-off, poor survival.

The animals that received cipro have a flatter and more successful looking survival curve.

Now, we can see that there are three deaths in the cipro cohort, and those have been discussed already. I just want to go over again briefly what those deaths represent.

There's one cipro death in this population, and that is the middle X. This is an animal that died of anthrax at day 36, that is, six

days following exposure.

There were two non-anthrax deaths in this population, as well. One animal died at day five from a drug administration accident. A drug was introduced into the airway, and one animal died at day 103, found to have urinary tract obstruction.

This second and third animal were examined both microbiologically and histologically and found not to have evidence of anthrax.

Okay. Next slide.

You've seen this one already, too. This is a summary set of survival curves for all six cohorts. I think, again, we can see there are two types of survival curves, the very steep ones presenting the data for the control and the vaccine only animals.

The four curves representing survival for animals that received 30 days of antimicrobial all show markedly better outcome.

The anthrax deaths in any of these animals all occurred between days 30 and 60 post exposure. There were three anthrax deaths in the penicillin

cohort at days 39, 42, and 50. There was one anthrax death in the doxycycline group at day 58.

Next slide.

The next two analyses I'm going to show present similar concepts as have been shown in the survival curves. If we look at an intent to treat analysis that goes out to 130 days post exposure and we look at all animals, all deaths, what we can see is that the survival rates of any animals who received an antimicrobial were statistically significantly better than those animals that did not receive an antimicrobial, that is, the control animal, so those who received vaccine only.

Inspection of the P values or the 95 percent confidence intervals around the differences between the treatment group and the control demonstrate the significance of these differences.

Next slide.

If we look at an analysis of the evaluable population of animals and look only at deaths due to anthrax, a similar conclusion can be reached. I'd like to point out that the evaluable populations for

two of these cohorts only contain nine rather than ten animals. In the ciprofloxacin group, there was the animal that died at five days because of a drug administration accident. This animal was considered unevaluable for the 90 day test of cure period.

Similarly, there was an animal that died in the doxy plus vaccine group, was found not to have anthrax, did not complete the 90 day study period, and therefore, was also considered unevaluable.

Calculation of the anthrax death rates shows us, again, that for any group that received 30 days of antimicrobial, there is a statistically significant better survival than those animals in the control group.

Okay. Next slide.

When we think about giving a drug for post exposure prophylaxis of this disease, an underlying question that arises very quickly is how long do we give the drug for.

From the early work of Henderson's group, we can see that a regimen of five, ten, or 20 days is too short. From the work of Dr. Friedlander's group,

a 30 day regimen certainly looks better.

At the same time, we need to consider that in that ten monkey cohort that received ciprofloxacin, there was one anthrax death six days following the cessation of therapy.

Now, we've seen a couple of other lines of evidence suggesting that spore loads decrease over time, and another way we might approach this duration of drug administration question is to ask if there is some spore load that can be tolerated by the human host such that the risk of disease is minimal. Is there a floor to the spore load?

Okay. Next slide.

There is some work in human epidemiologic studies that might give us some insight into the answer to this question. Published accounts of this Sverdlovsk outbreak of inhalational anthrax in 1979 state that the longest incubation period of a fatal case is 43 days.

Now, I think we do want to note Patient No. 42, who was mentioned earlier this morning. This is a man who was found dead of inhalational anthrax

about 60-odd days following exposure. The nature of his exposure and when he was exposed is not known.

There are other data looking at industrial exposures in non-immunized mill workers who have been found to inhale somewhere between 150 and 700 anthrax contaminated particles of a clinically relevant size every shift, and yet clinical disease in this population was quite rare.

Now, it might be reasonable to wonder if a population like these mill workers who are exposed to repeated low level organism loads might have some form of protection not conferred on a completely naive individual who is only exposed in a single, large aerosol dose.

This was looked at also in a separate group of studies which showed that the likelihood of development of anthrax in textile mill workers was independent of the duration of their employment, suggesting that the longer time you spent in the mill did not necessarily provide you with protection from disease.

Okay. Next slide.

So with inhalational anthrax, we have a rare, rapidly progressive disease with very high mortality. There is little opportunity to improve outcome with treatment once the clinical disease is recognized for what it is.

This organism has also been identified -- this disease -- excuse me -- has been identified as a clinical manifestation of a biological agent of highest potential concern.

Next slide.

There is currently no drug approved for prophylaxis of this disease. It can't be studied in humans, and we've seen a discussion of a non human primate model that demonstrates a similar pathology and mortality as has been seen in humans.

Next slide.

What have we learned about ciprofloxacin? Post exposure administration in a primate model of this disease was shown to significantly improve survival compared with placebo. Comparable blood levels can be achieved with the dose used for successful prophylaxis in the primate model of

inhalational anthrax with 500 milligrams administered every 12 hours to human adults and with 15 milligrams per kilo administered every 12 hours to children.

Blood levels achieved in experimental animals and humans are roughly 30 to 50 times the MIC-90 of the organism.

What we have seen of use and safety data for ciprofloxacin show us that it has a broad array of indications with substantial clinical experience and a well characterized and large safety database.

Next slide.

We might think of prophylaxis as an effort to reduce the risk of disease. From the animal model results that we have looked at this morning, we saw that ciprofloxacin survival was better than placebo following a 30-day regimen. Human epidemiological data suggests the duration of drug administration might be at least 45 days.

The duration of the proposed regimen is 60 days.

Next slide.

Question number one for the committee is:

do the data presented support the safety and efficacy of ciprofloxacin for post exposure prophylaxis of inhalational anthrax?

Question number two: if yes, is 60 days an appropriate duration of ciprofloxacin administration for this indication?

In closing, I would like to acknowledge the substantial work of my colleagues on the review team and the tireless efforts of our project managers.

Thank you.

CHAIRMAN RELLER: Thank you, Dr. Meyerhoff.

Are there any questions before we break for lunch for Drs. Meyerhoff or Chikami? Yes, Dr. Archer.

DR. ARCHER: Dr. Chikami said early on that programmed for large scale use of these drugs in civilian or military personnel required an approved NDA. Does that mean that penicillins and tetracyclines, which only have a treatment indication, cannot be used as prophylaxis?

DR. MEYERHOFF: If they are going to be

shipped across state lines.

DR. ARCHER: Meaning?

DR. MEYERHOFF: That they are not approved for that use, and that would be the activity we would regulate.

DR. ARCHER: Is there any reason why then they haven't been brought forth at the same time as cipro, to get an indication for prophylaxis?

DR. MEYERHOFF: I don't know the answer to that.

DR. ARCHER: You brought them forth. Why didn't you bring doxycycline up as well as cipro?

DR. MEYERHOFF: Gary, would you like to answer that?

DR. CHIKAMI: Yeah, I guess I'll answer that question.

(Laughter.)

DR. CHIKAMI: I guess as we've interpreted the treatment indication for penicillin and doxycycline, in fact, in those situations, we've interpreted that indication broadly so that in our discussions we felt, and Dianne can correct me if I'm

wrong, we felt that, in fact, in those situations an IND wouldn't be required.

DR. ARCHER: So, in fact, for this use it would be considered -- treatment and prophylaxis would be considered equal in the case of the drug labeling?

DR. CHIKAMI: That's how we've considered the situation for penicillin and doxycycline, and part of that is the historical nature of those indications. Those drugs were approved in the case of penicillin in the probably mid to late '50s, in the case of doxycycline in the '60s and '70s when indications were written quite broadly without attention to detail in regard to differentiation between prophylaxis and treatment, and products were given broad treatment indications based on data which were essentially case series.

So that given the broad clinical use of those products clinically and also clinically for the treatment of anthrax, not specifically inhalational anthrax, as you've heard, again, we've taken sort of a broad interpretation of those indications.

DR. ARCHER: So just one more follow-up.

So as an agency, governmental agency, would you consider ciprofloxacin, tetracycline, penicillin equal for this indication if you were being asked to give recommendations?

DR. CHIKAMI: Well, I think based on the information that we have in hand and looking at the data, I can't differentiate either certainly increased efficacy of one over the other. I think there are specific considerations that may lead you to choose one product over the other in a specific situation, and I think that's one of our purposes in bringing this forward, is to provide another alternative to the other two agents which have long historic use.

CHAIRMAN RELLER: At this point I'd like to suggest that it's exactly 12:45, that we break for lunch for one hour. There will be time to pursue all of these questions in relation to addressing the charge to the committee.

Please be back at 12:45 to begin the public -- excuse me -- 1:45 to begin the public hearing.

Thank you.

One more thing. If you follow either hallway, for those who are not familiar with this building, you will end up in the cafeteria on this floor.

(Whereupon, at 12:47 p.m., the meeting was recessed for lunch, to reconvene at 1:45 p.m., the same day.)

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

(2:07 p.m.)

CHAIRMAN RELLER: It's now time for the open hearing. We have one scheduled speaker, and this would be the appropriate time for relevant remarks, comments, raising of issues, but not the specific directing of questions to individual members of the panel, but the issues that would be considered in the subsequent discussion of the members of the Advisory Committee.

Also, as was done earlier with the members of the Advisory Committee, in fairness we ask that anyone speaking if they have a previous financial involvement with the sponsor or any other relevant financial disclosures to make, to please do so.

Thank you, and the public hearing is now open.

First we'll have Dr. Itzhak Brook speak.

DR. BROOK: Good afternoon. I'm Itzhak Brook from the Armed Forces Radiobiology Research Institute. I'm a past Chairman of this committee from 1984 to '88, and I really am happy to address it again

on a topic that I think is very pertinent, which is the resistance of Bacillus anthracis to antibiotics.

Some of them are being discussed today. It's obvious that we need to recognize the importance of the possibility of the development of resistance or selection of resistance during the treatment.

We have done some work, and some of it has been published a few months ago and some has not yet in trying to predict in an in vitro manner the subsequent induction of resistance to Bacillus anthracis, by Bacillus anthracis to the antibiotic that may be used for prophylaxis and treatment.

The method that we used has been tested before against other organisms, for example, streptococcus pneumonia, hemophilus influenza, by a variety of researchers. The most noted group that has done a lot of work is Dr. Appelbaum and Jacobs' group, and what we did is in vitro growing the organism in a sub-inhibitory concentration and selecting the first growth of the organism in the in vitro system and then sub-culturing it in another series of sub-cultures, and doing it seriously, seriously sub-culturing it for

21 sub-cultures.

And it's possible actually to extend it further than that, but what we did was sub-culturing it for 21 sub-cultures, and what we found is, and as you can see here, with an ofloxacin is that there was an initial, very low, minimal inhibitory concentration of about 1.25, but at about sub-culture number seven and eight, one strain -- we did it in duplicates -- stayed -- each of the strains doubled their MIC. One of them, the number 15 sub-culture, continued to increase its resistance, and by sub-culture 20 resistance was more than 3.2 micrograms per mL.

Next one.

Next we or simultaneously we looked also at ciprofloxacin. Here the MIC was also quite low, and here, too, about one of the strains at about sub-culture number five tripled its resistance, and another jump in resistance of both strains occurred at sub-culture 12 and another one at sub-culture 18, to end up in an MIC of 3.2.

We looked also at doxycycline -- I'm sorry -- at trivofloxacin (phonetic), and we looked at the

altro derivative, and here too with this new quinolone, the MIC was low, but again by sub-culture eight, nine there was a quadrupling of the resistance, and then afterwards at the number 12, the resistance was quite high.

We also looked at the possibility of cross-resistance between quinolones. We took the strain that became resistant to ciprofloxacin and tested it against gatifloxacin and it was cross-resistance. The strain that was resistant to ciprofloxacin was not affected in vitro by a newer class of quinolone, gatifloxacin.

In doxycycline, we saw very little change in resistance, only one tube dilution difference. The initial MIC was 0.025, a jump to 0.05 at the ninth transfer, and there was an increase to another tube to 0.1, but it did return back, and then again one strain stayed at 0.1. The other one is 0.5, which are clinically attainable concentrations.

However, with all of the quinolones that we've showed you so far, the subsequent resistance was about the same concentration that is achievable in

serum.

Next.

We are also right now looking at gatifloxacin. Unfortunately we just started to do it a short time ago, but at least by the eighth dilution there was one move. There was a change initially to doubling the MIC, and I think what has concerned us the most is that a strain that was becoming resistant to cipro also showed resistance to gatifloxacin.

So we would not be surprised if that would occur at later subcultures.

So this is the data that I wanted to show you, and I think that whatever consideration the committee would take in assessing the usefulness of the quinolones, this kind of information has to be taken into consideration that there is a possibility of selection of resistant organism.

The question, of course, is how likely is it to happen in clinical practice, and again, I don't have any way of answering that, but I think from looking at other organisms, that type of test does have the potential of predicting what may happen in

the future in clinical use of the drugs.

And just before finishing, I just want to bring more of a question to the members of the committee. The question that I brought earlier was whether there were any clinical trials in looking at ciprofloxacin or other quinolones in sporadic cases of Bacillus anthracis infection that occurs in many countries around the world.

Thank you.

CHAIRMAN RELLER: Thank you, Dr. Brook.

Are there any other persons who wish to present comments to the committee for consideration in their discussions?

(No response.)

CHAIRMAN RELLER: If not, the public hearing is closed.

It's time for then the break on the agenda, which we've already just taken.

(Laughter.)

CHAIRMAN RELLER: And, Dr. Chikami or Dr. Meyerhoff, do you want to formally present the charge to the committee or we'll just go ahead and address

the questions?

DR. SOPER: Barth, can I just make one statement or comment?

CHAIRMAN RELLER: Sure, Dr. Soper.

DR. SOPER: As Dr. Brook has pointed out, it's pretty easy to induce resistance in these microorganisms, and I'm not an expert in bioterrorism, but if I was going to use this microorganism as an agent for bioterrorism, why in the world would I use one that was sensitive to penicillin, doxycycline or ciprofloxacin? And how is this element of prophylaxis relevant?

In other words, if you are using an -- if you know what the agent is sensitive to, why would you develop a bioterrorist agent that was sensitive to anything that somebody has to counteract it?

DR. CHIKAMI: I guess I certainly wouldn't consider myself an expert in sort of strategic planning of developing a biological weapon. I guess my own perspective on this issue is that given the information that we have in hand and the overall motivation, that is, to provide what we view as at

this point in time reasonable alternatives to a potential response to this issue, that -- and this is what I've sort of decided in my own thinking -- is that understanding that a completely resistant organism is a risk in this situation, even given that scenario, what we understand about the usual antimicrobial susceptibility patterns of the organism and the data that we have in hand, is it reasonable to consider -- to determine that this agent or penicillin, whatever, this agent is reasonably likely to be useful in that situation, understanding that as with the treatment of any infectious disease, once the situation arises, the final determination of the use of an agent will be based on susceptibility testing.

I mean I think that's all we can do in this situation.

DR. MURPHY: I want to try and clarify the prior question also. Basically, at this point, as I tried to indicate in the introduction, we feel that if one needs to utilize the other two products that have been presented, the class of cillins and tetracyclines or doxycyclines, that one has that organism therapy in

those -- treat those anthrax in the label at this time, and that we would have no difficulty with that product being shipped for the treatment of that organism.

Now, the next question is: well, why do we ask this company to come in with this product? And that the reason is that we understand that we have no indication in the label for this organism in this product. We also understand that resistance could be something that a terrorist might do, and that the knowledge that we're aware of is that there are organisms, anthrax organisms that have been altered to be penicillin and tetracycline, doxycycline resistant. Do that mean that they couldn't also be cipro resistant? Clearly they could be if somebody wants to make them.

Our goal today is to provide another option, and we want the committee to consider does the evidence that we have brought forth support providing an indication in this label so that there would be an additional option to therapy.

I think in any situation the

recommendation would be if you knew the sensitivities, you'd treat it with a drug that you knew it was sensitive to. It is the concept of trying to have a number of options available.

CHAIRMAN RELLER: I might add yesterday in an open public meeting at the Microbiology Devices Panel of the Food and Drug Administration, experts from the Department of Defense, the CDC, and academia, others addressed the issues of the latest and best technology, what would be done to rapidly recognize an exposure that would put the public or individuals at risk and the mechanisms for rapidly confirming, including susceptibility testing.

And actually this was mentioned in the Bayer presentation of an important component if such a tragic event were to occur is to delineate what might be an altered organism and then take the appropriate steps thereafter.

I think it would be effective to at this time, since there were some possible lingering questions, while all of the invited guests, experts with extensive experience, that this would be an

opportunity for the voting members of the committee to raise those questions, and basically it's quite straightforward, the questions being asked of us, and we will vote yes or no with the best advice that we can give to the agency about this application based on the data available.

But now would be a superb time with the invited experts to raise any -- to seek any additional information that the committee members would like to have before they vote on the questions at hand.

David.

DR. SOPER: I have just one question about the duration question. It seems to me there was that one case that was 43 days and no further -- why are we going 60 instead of, say, 45 days? I mean is there some sort of standard deviation or this is our best guess?

CHAIRMAN RELLER: Mr. Verderame?

MR. VERDERAME: The reason that Bayer chose to propose 60 days' duration was honestly based on the working group consensus statement which was published in JAMA and which those experts recommended

60 days.

CHAIRMAN RELLER: I think it's beyond the latest recognized with a few days' margin to come to an even number.

Thank you.

Dr. Deitchman and then back to Dr. Walker. Yes, please.

DR. DEITCHMAN: Thank you.

I'd like your indulgence to finish a question that I didn't get a chance to ask before we broke for lunch, and that was to help me understand how this NDA, if approved, would relate to this question of prophylaxis versus treatment of clinical disease, particularly since it seems to me that in a patient with a known or presumed exposure who presents with flu-like symptoms, at that point you're no longer talking about prophylaxis. That patient is being treated to prevent progression of disease.

So you have a spectrum that ranges from prevention of first symptoms, treatment of early symptoms, and treatment of overt clinical disease. How would this NDA relate to approval for treatment?

DR. MURPHY: Let me try this. The need to treat a patient if you have a product on hand for something that's not on the label is the practice of medicine, and as indicated, we would not regulate that.

We are not -- we don't think that we would have the opportunity to study all various manifestations of this organism as a disease. We need the ability to say that we have the indication to treat what we think will be the most common situation.

Could be wrong. You're right, but it is the thought at this time that if this organism was used, it would be used as an inhalational event, and that if product were needed, it would be sent to treat the population that had been exposed.

Now, if people have a fever are we going to say they can't have the medicine because the doctor there would not be able to give them the therapy at that point? Certainly not. It is the ability to have an indication that would be for the treatment of this or the prophylaxis exposure that would allow us to have this product.

DR. DEITCHMAN: And I guess to amplify on that point, what you've described is a situation of post exposure prophylaxis. There's a very fine line between what you might consider early treatment as opposed to post exposure prophylaxis, and that's sort of the territory we're in as opposed to primary prophylaxis, which is not what we're talking about.

DR. MURPHY: And we had a number of discussions about how we would describe this, and I think you all are struggling. What we're trying to relay is that the intent is where do we think it's going to be used. Where do we think we have the most information? That's what we would label the product for.

And people would use the -- as always, the physician would have discretion to use it as they needed to.

CHAIRMAN RELLER: Dr. Archer.

DR. ARCHER: Can I just add a possible scenario? I'm trying to get an idea of how this would work.

What if somebody calls up, for instance,

a local television station in Washington and says, "I am Joe Schmo, and I've just released anthrax into the Washington area"? At what point does this trigger a response, and what is the response of the appropriate agencies going to be in terms of what antibiotic to recommend for immediate post exposure prophylaxis?

DR. MURPHY: The FDA is not deciding that.

DR. ARCHER: Well, they might turn to you for recommendations though on which antibiotic is --

DR. MURPHY: There will be -- there are recommendations, and I think the CDC is very much involved with that, and we really are trying to stay clear of what is stockpiled for what by whom. We're simply saying we know what the products are that will possibly be recommended, and we need to be able to look at whether we can make them available or not.

So that's sort of the task that we have before us today. We would not be telling the DOD or anybody else that they should ship this or shouldn't ship that.

CHAIRMAN RELLER: Along those lines,

again, from the meeting yesterday, I mean, there's an interagency including working with the Infective Diseases Society of America and others that led to that statement, but CDC, the Department of Defense, civilian authorities, police departments, their federal grants, you know, for preparedness for this and other public health emergencies, and again, the question that we're going to be dealing with is based on the scientific evidence that we have heard this morning and is available in the literature for the purpose of recommending or not to the agency that ciprofloxacin be approved for use in the setting of inhalational exposure and for prophylaxis after that, most plausibly associated with a bioterrorism event, but it theoretically could be in other situations where such a personal or public health emergency, accident were to occur.

Yes, Dr. Takafuji.

COL. TAKAFUJI: Yes, this is Colonel Takafuji.

From a DOD perspective, I think I need to clarify some things. Scott is absolutely right. I

want it clearly understood by everyone that CDC and DOD are really together on this issue. It's not two positions, although their interest is more from the standpoint of the civilian public health issues, whereas ours is more from the position of our Armed Forces.

But there is concern about stockpiling. There are decisions that have to be made about stockpiling, the amount, the quantity, the location, all of those things that come into play. There are even cost issues that come into the equation.

But what we are talking about clearly is post exposure prophylaxis, and the word "prophylaxis" has been loosely used, but it is really not our intent to extend any package labeled use to the pre-exposure scenario because I understand, and we have had legal advice given to us as you have here at FDA pertaining to that fine line in terms of pre and post exposure. There are clear differences in terms of how that would be interpreted and how you would have to address each scenario.

So from the standpoint of CDC and from the

DOD, if I could just kind of paraphrase and follow onto what Scott said, we are clearly talking about after an event has occurred, and the use there. Right now without the labeled use, it really hampers our ability to be able to respond, to be able to have the right amount of antibiotics at the right place at the right time.

And it doesn't make any difference whether we're talking about civilians or are we talking about military personnel?

CHAIRMAN RELLER: Yes, Dr. Chesney.

DR. CHESNEY: I know the information about treating anthrax with penicillin and doxycycline is old, but was that patients who actually had pneumonia or was that based on MICs? Do you know?

DR. CHIKAMI: It's very difficult to reconstruct that information, and given the epidemiology, again, I would suspect that inhalational anthrax was not included, represented very broadly in those patients. Primarily cutaneous.

CHAIRMAN RELLER: Dr. O'Fallon.

DR. O'FALLON: My concern is maybe I've

got this wrong, but I have this idea, to use your thing, that somebody goes up to the top of the Washington Monument and dumps some stuff out, and so that would seem like unless you guys have got a pretty good idea of where the winds are blowing and all of that, you're probably going to have to treat an awful lot of people.

All right. Now, some of them are children. We were told -- I don't have a real clear idea of the safety profile for 60-plus days of treatment. We're going to be treating an awful lot of people that really don't need it, but we can't distinguish who they are.

So my first concern is that a really long term toxicity profile because there are a lot of not sick people that are going to get this stuff. So that's a do no harm type thing. Of course, it's between that and dead, you know.

(Laughter.)

DR. O'FALLON: I work in Cancer. I've got that real clear.

(Laughter.)

DR. O'FALLON: But it is an issue, and so the first thing I'd like to ask -- well, there are two issues that are of concern. One of them is the long term, really long term safety profile because when you dump them all together, if only ten percent of the patients have been treated long term and the other 90 percent were short term, the toxicity profile that you see in the combination is the short term. The others don't even show up on the radar screen.

So that's the first thing I'm concerned about, and the second thing I'm concerned about is how dependable is efficacy information in primates for predicting for human beings because that's where our data are, the efficacy data.

COL. TAKAFUJI: If I could just make a comment, I think it should be remembered that not only will you not be able to know exactly who was exposed. You also will not know how much they had been exposed to. So there are a lot of assumptions and there will be a lot of confusion and so forth.

I think everyone understands that. The Office of Emergency Preparedness, as you probably well

know, has been addressing this and looking in terms of what's the right approach that should be taken in this country, and DOD and CDC and many other agencies are very much involved in that in terms of the national plan of response.

But there will be some uncertainties, but again, just to reiterate and to keep it within the scope of this meeting, what we are interested in is the specific indicated use that will allow us to at least have the option. Otherwise we'll be writing a lot of prescriptions.

CHAIRMAN RELLER: We have several questions. One, again, of the emphases in yesterday's meeting was how important it was just to confirm, separate out hoax from real threat very swiftly.

Jonathan Moreno had a question, but maybe before that because if it has to do with the safety issue, there were data presented by the sponsor earlier. I mean another way to look at the 90-10 was a much smaller, maybe even less than ten proportionately had, but there were safety data presented in the subset that -- the smaller number,

but yet extensive number. Please.

DR. POSNER: Yeah. It might be helpful to just put that overhead back up because we did break it out up to 30 days, 30 to 60 days, greater than 60 days, and, yes, you're right. Dr. O'Fallon is right. The numbers are smaller, but there are still, I believe, over 100 patients and maybe beyond that.

There's a lot of data on that slide, I know. So we'll just reshow that one if you don't mind.

CHAIRMAN RELLER: It's an important question. So we'll get this sorted out.

Actually while that's being found, since we won't forget it, maybe rather than in a rush you can take your time, find the data, and we'll hear from Jonathan Moreno.

MR. MORENO: Thank you.

Stimulated both by Dr. O'Fallon's first point and also by Mr. Verderame's statement this morning that cipro was distributed in the Gulf War, something that I didn't know until just this morning, and I've been following -- I thought I had been

following the anthrax issue in the Gulf pretty closely, has the -- and I guess this is really a question for Colonel Takafuji to some extent -- has the DOD satisfied itself that it's done what it can with respect to a look-back to gather whatever information might be available with respect to who took cipro, how many people did, and what the experience was?

COL. TAKAFUJI: As far as the data in terms of how well that was tracked and so forth, I'm not sure we really have that good of data, except I can tell you that although it was distributed, much of it was not really used. In fact, most of it; just about all of it was not used because we never had the incident. It was more an issue of preparedness.

MR. MORENO: Right. It just occurs to me that if even a few hundred people used it for some time --

COL. TAKAFUJI: I don't think we even have that experience.

MR. MORENO: If I were a member of the Advisory Committee, I guess, I would want to satisfy

myself that the DOD had done what it could to do a look-back with respect to that population.

COL. TAKAFUJI: Well, cipro is a pretty widely used drug. If you wanted to just collect safety data on use, and you remember the use of cipro would be relatively short term in that scenario anyway. I'm not sure that would be the best population to collect safety data on, frankly.

But I can tell you that from a DOD perspective that a lot of thought was given into the discussion to distribute ciprofloxacin, but since that time we have come to realize that it's just not a simple matter just passing out pills. It requires everything that has to be adhered to from a strictly regulatory perspective, and that's why we are concerned.

And cipro represents one, of course, of many antibiotics that could be used.

MR. MORENO: Thank you.

CHAIRMAN RELLER: Yes, Dr. Deitchman.

DR. DEITCHMAN: While we're waiting for the visuals, perhaps one other vulnerable

subpopulation we haven't talked about is asthmatics who are receiving theophyllines or other zanthenes. Some of the material we received ahead of time talked about concerns that due to competing metabolic pathways these folks who then take ciprofloxacin may be at risk for theophylline toxicity, and I wonder if representatives from Bayer could provide us any guidance on what recommendations might be made for those patients in this kind of situation.

MR. MONTEAGUDO: Yeah, you're absolutely correct. This is something that's mentioned in the patient -- in the package insert for ciprofloxacin, the interaction with theophylline, and theophylline levels can rise with co-administration with ciprofloxacin.

In terms of what advice to give out, I think it should just be good medical judgment in terms of monitoring theophylline levels or possibly making a decision as to what would be the appropriate antibiotic to use.

CHAIRMAN RELLER: Dr. Archer.

DR. ARCHER: What is the shelf life of

cipro? If it were stockpiled, how often would the stockpile have to be replaced? Does anybody have that data?

DR. POSNER: The shelf life is two years -- three years. Sorry.

DR. ARCHER: So in terms of stockpiling, you would presume that the stockpile would have to be turned over every three years if it weren't used?

DR. POSNER: I wouldn't be able to make that kind of a decision. Cipro is generally used acutely. So that issue has really never come up.

DR. ARCHER: Can anybody speak to the stockpile issue and the stability of that versus doxy. and penicillin in terms --

CHAIRMAN RELLER: Gordon, again, you know, I mean the facts are -- I mean, you know, the shelf life is two years. Now, how the DOD, the CDC, the national stockpile and others deal with that, you know, I mean, that's not our purview.

DR. ARCHER: It's a curiosity question.

CHAIRMAN RELLER: Right. And in the interest of time, yours and everybody's we'll go to

the safety data.

DR. POSNER: Yeah, we have the technology working now. So maybe that's a good time to just not press our luck and turn to the data that we have here, and you can see we've tried to break them out.

These are the adult patients. We also have it done for pediatrics as well, and you can see that we have put them into groups. The first two columns are controlled clinical trials. So we have about 24,000 patients in controlled clinical trials.

The other includes both controlled clinical trials and uncontrolled trials. So it's not quite the same population, but we do have about 1,400 patients treated out between 30 and 60 days, and 1,000 patients treated out beyond 60 days, and in general, the adverse -- these are adults -- in general, the adverse event profiles are similar whether you go up to 30, beyond 30, or up to 60.

MR. VERDERAME: I would like to add one other point for the committee's -- just for their general knowledge, that ciprofloxacin is already approved up to 42 days of treatment for bone and joint

infection. So it's not that much more of a leap to go to 60.

CHAIRMAN RELLER: Dr. O'Fallon, that's what there is. Any other question?

DR. POSNER: We also have that for pediatrics because I know of Dr. Christie's interest in children. Maybe you just want to show to comparable slide for children.

We don't have quite as many children, but we do have over 100 in each group, 2,300 for all patients. Again, we have 190 patients, roughly 38 to 60 days, and 104 patients out beyond 60 days. Once again, there's really not much of a difference in the adverse event profiles.

CHAIRMAN RELLER: Thank you.

For our invited guest experts, is there anything that if the committee has not asked, you think that they should consider in their vote on the questions at hand?

DR. WALKER: I'd like to bring up you discarded the cases of --

CHAIRMAN RELLER: Use the mic please.

DR. WALKER: You've discarded the case of the patient who was out over two months, and I'm not -- there were never any inhalational cases of anthrax before this event. There have never been any after that event. I believe that patient was related to this event. I believe that patient died within a day or two of the time that they were found, and I believe that it's possible that spores, if they can remain in the soil for as long as we've been told, that they can remain in a patient for longer than the 42 or 43 days.

Now, with prophylaxis you're never going to cure everybody. You're never going to prevent everybody from getting the illness. It's just a numbers game, and where you decide to draw the line is going to be fairly arbitrary.

But I believe that the 60 days is not an unreasonable number, and I think Art may have a different opinion.

DR. FRIEDLANDER: No.

CHAIRMAN RELLER: Dr. Friedlander.

DR. FRIEDLANDER: No, no ,no. I agree for

prophylaxis. Remember these primate studies are done with eight LD-50. If you put that up by a log, the possibilities of disease occurring even later certainly exist. I mean it's certainly logical. So I don't think 60 days is untenable or unreasonable.

But the exact point, as has been pointed out here, is somewhat arbitrary.

CHAIRMAN RELLER: Yes, Jonathan Moreno.

MR. MORENO: If an event takes place, will the different government entities that might have to use the stuff have different rules for monitoring the results?

I mean that's clearly the opportunity, unfortunately, to learn in situ how well this or any other medication works. What can the FDA require with respect to reporting of the results, monitoring, and so forth?

DR. MURPHY: Again, we're not the CDC, but from what we understand, that there will be efforts, and my understanding is fairly sustained and very vigorous efforts, to track who receives medical along the concept of a large, simple trial.

You're not going to be able to have details of lab tests or minor clinical symptoms, but you know, who died, who was in the hospital.

I would suggest that asking us any more about how that large, simple trial would be implemented at this point would probably not be fruitful, but I certainly think that those discussions are ongoing about ways to make sure that in an event, that whatever product is used, irrespective of the one we're looking at or under an IND, that who receives drug and what happens to them is tracked in the most vigorous manner.

I mean, I guess we should invite if there's somebody from the CDC who would like to comment on that, but that's my understanding at this point.

Gary, do you have anything else?

CHAIRMAN RELLER: Dr. Hugh-Jones, is it a comment on this point or a different one?

DR. HUGH-JONES: Well, it's basically the same point.

CHAIRMAN RELLER: Okay.

DR. HUGH-JONES: Being a vet, I'm somewhat more robust about losing my patience than medics are. I have to be. It's a fact of life.

But in the Sverdlovsk exposure, our general feeling is that it was something less than one LD-50 that was disbursed as far as normal exposure, people walking through. Obviously it was more than a number of LD-50s if they just stood out there breathing all the time, but in the normal, average exposure, it was less than one LD-50.

And, therefore, this modest amount of antibiotic that they were given was fairly adequate. Plus on the 22nd of April, they went in and vaccinated and had very good vaccine cover at least for one shot. So that was seven days -- 12 days after the diagnosis they were vaccinating, and I think they covered 80 percent of the population.

So what I would say is that when you have an exposure, you've got to come down to what is the expected dose that people are getting, dividing your population into not exposed, possible, probables, and certainties.

The certainties obviously should get the full 60 days, but do you have enough infrastructure in a city with, say, 500,000 people to give them 60 days' coverage, you know? You've got to cut your cloth and assume some losses at some point.

This issue of follow-up is an interesting one, but another perspective that might be worth considering is that the presentation has many unique features, as has been pointed out, and clearly instead of an individual diagnosis, there's a public health, governmental responsibility for which an enormous amount has already been invested for early recognition, confirmation, and similarly already discussed is the obligation on the part of the same public health infrastructure to do the appropriate follow-up should a public health tragedy occur.

And that is quite a different thing from thinking in terms of post approval studies in a different context that would be -- enough said.

It's time for the questions, I think, unless there are any other comments. Shall I read them?

Question number one for the committee: do the data presented support the safety and efficacy of ciprofloxacin for post exposure prophylaxis of inhalational anthrax?

We'll go around the voting members. Dr. Archer, you have the first opportunity to vote.

DR. ARCHER: Such as the data are, with the understanding that they're not likely to ever be better, and it's an unusual indication, I would say yes, also with the understanding that ciprofloxacin is one of currently three acceptable agents for post exposure prophylaxis. With the data given, no better or no worse than the other two, I would say yes.

CHAIRMAN RELLER: Thank you.

Dr. Chesney.

DR. CHESNEY: I say yes. I just wondered if we wanted to add caused by susceptible strains, the point being that you would know that after a few days. Would one continue prophylaxis for 60 days knowing it was a highly resistant strain?

DR. CHIKAMI: No, and I think you're familiar with the way we usually write our indications