UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL

PRODUCTS ADVISORY COMMITTEE

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MEETING

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WEDNESDAY, MAY 27, 1998

The meeting took place in Versailles rooms I and II, Holiday Inn, 8210 Wisconsin Avenue, Bethesda, Maryland, at 3:40 p.m., Patricia L. Ferrieri, M.D., Chair, presiding.

PRESENT:

PATRICIA L. FERRIERI, M.D.	Chair
NANCY CHERRY	Exec. Secy.
REBECCA E. COLE	Member
ROBERT S. DAUM, M.D.	Member
KATHRYN M. EDWARDS, M.D.	Member

CAROLINE B. HALL, M.D.	Member
ALICE S. HUANG, Ph.D.	Member
KWANG SIK KIM, M.D.	Member
GREGORY A. POLAND, M.D.	Member
DIXIE E. SNIDER, Jr., M.D.,MPH	Member
THEODORE EICKHOFF, M.D.	FDA Consult.
GEOFFREY EVANS, M.D.	FDA Consult.
DAVID KARZON, M.D.	FDA Consult.
SANDY ROVNER	FDA Consult.
Dr. NORMAN BAYLOR	Speaker

PUBLIC COMMENT:

DR. PETER PARADISO

JOHN SALAMONE

MICHELLE SAVALOS

DR. LAUREL HALSTEAD

DR. JOHN LEVENGOOD

MIRIAM O'DAY

ALSO PRESENT:

KATHRYN ZOON, Ph.D.

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P R O C E E D I N G S

3:40 p.m.

CHAIR FERRIERI: I appreciate all those individuals who can stay, and would just reinforce what Ms. Cherry has sent out to you. Those who need to hear it the most aren't here to hear it now.

The session as I indicated, is dedicated to the boxed warning on the package insert for oral polio vaccine and an overview of the issue will be presented by Dr. Norman Baylor from FDA. Following that there will be another public hearing.

DR. BAYLOR: Thank you, Pat. The Office of Vaccines Research and Review, Center for Biologic Evaluation would like to present to the Vaccines and Related Biological Products Advisory Committee the issue of including a boxed warning for a vaccine associated paralytic poliomyelitis in the package insert for live, oral polio virus vaccine.

Moreover, in light of the fact that boxed warnings have been rarely included in labeling in biological products and not included in labeling for vaccines, the FDA would like the VRBPAC to consider and comment upon the utility of including a boxed warning for a vaccine associated paralytic polio in the package insert for live, oral polio.

Further, the FDA would like the committee to discuss the scientific criteria to be used in determining whether a boxed warning should be included in the labeling for a live, oral polio vaccine, and how these criteria should be evaluated in determining if additional adverse events warrant inclusion in a boxed warning.

Now, I'll give in the first slide, an outline of the presentation. What I'm going to try to cover briefly in considering the boxed warning on the package insert, I'm going to briefly discuss the background on the risk of vaccine associated paralytic poliomyelitis, then I'll discuss and comment on the citizen's petition to include a boxed warning to our vaccine associated paralytic polio.

I'll discuss the current package insert for oral polio, as well as talk about alternatives to a boxed warning that are already in place. I'll briefly comment on the impact that a boxed warning will have on promotional labeling and then I'll restate the charge to the committee.

The vaccine associated paralytic polio as many of you know, is a rare, adverse event which may follow vaccination with live, oral polio virus vaccine. The mechanism of that is believed to be a

mutation of a live, oral polio virus vaccine.

The mechanism is believed to be a mutation or reversion of the vaccine virus to a more neurotropic form. Reversion occurs in almost all vaccine recipients but it only rarely results in paralytic disease.

Vaccine associated paralytic polio is more likely to occur in those greater than 18 years of age than in children, and is much more likely to occur in the immunodeficient children than in those who are immunologically normal.

Compare it with the immunocompetent children, the risk of that is about 7,000 times higher for persons of certain types of immunodeficiencies.

The number of vaccine associated paralytic polio cases have remained relatively constant since the licensure of the vaccine in 1963, at about between five and ten cases per year. There's some evidence that this is even declining further to around three to five cases per year.

Between 1980 and 1996 there were over 300 million OPV doses distributed. In that period there were 142 total cases of vaccine associated paralytic polio, giving an overall risk of about one case per 2.5 million doses of vaccine. And of course the risk

varies by dose. The risk is about one case in 790,000 first doses administered.

For the immunocompetent recipients you'd have about one case of vaccine associated paralytic polio in every 1.5 million first doses, while for normal contacts it's about one case reported for every 2.2 million doses given. After later doses the risk is about one case per 25 million doses for recipients.

According to the CDC, during the period of 1980 to 1994, vaccine associated paralytic polio was investigated and characterized quite well. And during that period there were 49 healthy recipients of OPV coming down with vaccine associated paralytic polio.

Of the healthy contacts of those OPV recipients there were 40 cases of that: six cases were community acquired; 30 of those cases were in immunodeficient persons; giving a total of 125 cases of vaccine associated paralytic polio during this period.

If you break out the 30 percent or the 30 cases in the immunodeficient population, there's about 76.6 of these individuals who are immunodeficient -- and that number was about 23 out of the 30 were immunodeficient -- none of whom were known to be immunodeficient before receiving the vaccine. The

remaining seven immunodeficient cases were contacts of vaccine recipients.

Now, as many of you are aware, the agency recently received a citizen's petition to include a boxed warning in the package insert for oral polio vaccine. The petition requests that the FDA require the following boxed warning in the OPV package insert -- and this is the wording here.

"There exists a rare risk of vaccine associated paralytic poliomyelitis in individuals receiving live polio virus vaccines and in persons in close contact with them. The risk of contracting that is greater after administration of the first dose than after later doses."

Now according to the petitioner, "The boxed warning requested herein will advise physicians, other health care workers, and parents in a more prominent manner to help assure that direct risks of vaccine associated paralytic polio from OPV is clearly understood so that a better, informed decision of the use of OPV can be made by physicians and parents".

The package insert for pharmaceuticals is generally designed as a professional label. This labeling is geared toward -- primarily towards providing instructions to health care providers in

administering that given pharmaceutical. And in fact, the package insert is really not given to the recipient of the vaccine and that's requested of the health care provider.

Now, there's specific requirements for the content and format of the warning section of the package insert described in Chapter 21 of the Code of Federal Regulations under 20157(e).

And it states for a boxed warning, "special problems, particularly those that may lead to death or serious injury may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.

"If a boxed warning is required its location will be specified by the Food and Drug Administration. The frequency of these serious, adverse reactions and if known, the approximate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the Adverse Reaction section of the labeling".

"The function" -- now this is specifically

a part of the regulation that deals with the boxed warning. "The function of the Warning section of the drug's label is to describe serious, adverse reactions and potential safety hazards, as well as limitations to be used and imposed by them, and steps that should be taken if they occur.

"In general, the purpose of a boxed warning is to emphasize certain contraindications and adverse events which may be fatal or disabling when evaluating the risk versus benefits for use of a drug. Notwithstanding, in order not to dilute the effectiveness of a boxed warning, it is to be used only when special circumstances necessitate such additional emphasis".

And the operative, in this section of the regulation is, "special problems may be required by the Food and Drug Administration to be placed in a prominently displayed box".

I'm going to show you a couple of boxed warnings that we currently have in the agency. This is a product that is approved by lots of therapeutics in CBER. Now, this is for proleukin. And it's described here in a box warning.

"Proleukin for injection should be administered only in a hospital setting under the

supervision of a qualified physician. Proleukin administration has been associated with capillary leak syndrome. Therapy with Proleukin should be restricted to patients with normal cardiac and pulmonary functions."

This is just one example of a boxed warning where it talks about limitations of use. It also describes serious, adverse events or potential safety hazards.

If I could have the next overhead on the boxed warning that was approved for adriamycin, and this is an anti-tumor drug. This was approved in our Center for Drugs.

Here we have, "Severe local necrosis will occur if there's extravasation during administration. Myocardial toxicity manifested in most severe form by potentially fatal, congestive heart failure may occur during therapy or months or years after termination of therapy".

These two examples are therapeutic products. They're not vaccines, as I said. Currently there are no boxed warnings in the labeling for vaccines.

What I'd like to do now is, let's focus in on the package insert -- the current, approved, package insert -- for the oral polio. And in the

Warning section of the currently approved, oral polio labeling it states: "In 1993 the Institute of Medicine conducted a review of adverse events associated with childhood vaccines, including OPV. the IOM concluded that there's a causal relationship between OPV and paralytic poliomyelitis which is known to occur on rare occasion in vaccinees and their close contacts.

"In addition, the IOM concluded that OPV very rarely has caused paralytic poliomyelitis in immunocompromised persons".

So here's an example of where the package insert does include a statement warning against -- or the potential of vaccine associated paralytic polio. This does not appear in a boxed warning but it is spelled out quite specifically in the Warning section.

And if we look at the next slide, under the Adverse Reactions section of the package insert it says, "Prior to administration of the vaccines the attending physician should warn or specifically direct personnel acting under their authority, to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the risk and benefits of the vaccine, including the possibility of vaccine associated paralysis, particularly to the recipient,

susceptible family members, and other close, personal contacts".

So as it stands now, the package insert for oral polio discusses the vaccine associated paralytic polio in the Adverse Reactions section as well as the Warning section of the package insert.

In the next slide, if we look at the polio vaccine information sheet, by law, parents and guardians or patients must be given information in writing about the risks and benefits of vaccination before a vaccine is administered.

Moreover, under the National Childhood Vaccine Injury Act, Section 2126 of the Public Health Service Act, "All health care providers in the United States who administer any vaccine containing diphtheria, tetanus, pertussis, measles, mumps, rubella, or polio vaccine shall, prior to administration of each dose of the vaccine, provide a copy of the relevant vaccine information materials that have been produced by the Centers for Disease Control and Prevention".

Now, if we look at the information sheet for polio vaccines -- and I've excised this out of the vaccine information sheet -- one statement says, "On rare occasions OPV can cause polio because it contains

live, but weakened virus. IPV cannot cause polio because it does not contain live virus.

"Advantages: with four doses of IPV does not cause polio. Risk: for four doses of OPV, causes about eight cases of polio each year. This can happen to children who get OPV or people who are in close contact with them. The risk of polio is higher with the first dose than with later doses".

Now, this is required to be given to the parent, guardian, or the recipient, by law. And it clearly states that there is a risk of acquiring vaccine associated paralytic polio.

Other sources of information on vaccine associated paralytic polio and OPV that are readily assessable to health care providers as well as to the general public, are the American Academy of Pediatricians Red Book, the Report of the Committee on Infectious Diseases. There's a section that discusses the use of OPV and IPV as well as the risk of acquiring vaccine associated polio.

The MMWR's recommendation and report of the ACIP or Advisory Committee on Immunization Practices. This document also contains information on the risk of acquiring vaccine associated paralytic polio from OPV.

In this slide I just wanted to remind people

that there's also an impact on promotional labeling when there's a boxed warning in a product. Any reminder advertising such as giveaways, calendars or what-have-you, these cannot be distributed without a full package insert included or contained in the material.

This is because of the boxed warning. So either that boxed warning must appear on that giveaway or a full package insert must be distributed with that reminder advertisement. Journal advertising inserts may be required to include the actual boxed warning or a summary of the information contained in the boxed warning.

No brief advertisements can be used; only the products named in journals, magazines, or newspapers. So to mention this particular product, that is, oral polio virus vaccine, in a journal or magazine, it must be accompanied with the boxed warning if the product is so deemed to have a boxed warning.

Now, I want to return to the charge to the committee. The FDA would like the VRBPAC to discuss and advise the agency on the utility of including a boxed warning for a vaccine associated paralytic poliomyelitis in the package insert for live, oral

polio virus vaccine.

Further, the FDA requests that the VRBPAC consider possible scientific criteria for determining whether a boxed warning for vaccine associated paralytic polio should be included on the OPV label. If the VRBPAC members believe that a boxed warning is warranted for vaccine associated paralytic polio, we ask that you also comment on how the criteria for this decision could be applied to other vaccine adverse events.

Thank you.

CHAIR FERRIERI: Thank you. We could leave that up perhaps, Norm, so we could refer to it and be very concise, then. We have to move on to the open public hearing next before we do any discussions. And Mrs. Cherry will take over.

MS. CHERRY: We do have some individuals who have asked to speak at open public hearing. I would ask that you state for the record, your name very clearly; also, any affiliations,please, so that this can become part of the record.

The first name I have is Dr. Peter Paradiso.

DR. PARADISO: Good afternoon. My name is Peter Paradiso. I'm from Wyeth Lederle Vaccines and Pediatrics. I'm here obviously as a representative of

a company that makes vaccines for routine use in infants and young children, including oral polio vaccine, and as a person who is committed to the development and introduction of the vaccines in children.

The position of my company and of other manufacturers are fairly well documented in letters that have been submitted to the docket, either by us or in conjunction with other manufacturers. And I believe you have copies of those letters.

So I'm going to be brief with my comments because I think that our position and our concerns are fairly well outlined in those letters.

We're opposed to the use of a boxed warning for oral polio vaccine and for other routine, pediatric vaccines. My understanding is that a boxed warning is reserved, and as we just heard, for special problems or circumstances for which risks are not generally known and which require an extraordinary form of notice.

The boxed warning or a boxed warning, talking specifically about oral polio vaccine, would clearly go against current recommendations for the use of this vaccine's recommendations endorsed by the ACIP, the AAP, and the AAFP, who in deliberations over

the last several years in rather extensive deliberations, have concluded that in fact, it is still important to continue to use oral polio vaccine, particularly for its mucosal immunity, or the mucosal immunity that it induces.

And so the use of oral polio vaccine is still considered important for control of polio in the United States, and obviously, it's the main player in eradication of polio around the world.

Recommendations for use of a vaccine routinely obviously is a risk/benefit assessment. I think that unfortunately no vaccine is completely without risk, and clearly those risks are considered by these committees in determining whether to use a vaccine routinely. And I think a boxed warning is somewhat antithetical to a routine use recommendation of the vaccines.

As part of that and as part of that assessment, I think it's also important to note what Norman already has stated pretty clearly. Is that the risk of oral polio vaccine is very well documented. There are materials that are provided to parents and to providers.

Those are in large part, CDC-developed documents that in fact, taken into consultation, not

only experts but consumers in generating materials that will convey the risks without overstating the risks and without scaring parents -- particularly parents but also providers -- from the use of products that are considered to be important.

I think lastly, and the last point I think, what was mentioned by Dr. Baylor, the risk of vaccine -- this is not zero, and so a boxed warning for rare, adverse events will implicate other vaccines that are currently used routinely in childhood vaccines.

And I think that if a boxed warning is recommended for the oral polio vaccine it will set a precedent for recommendations for other routinely used vaccines, and clearly over-emphasizing the risks of childhood vaccination will reduce compliance in the use of vaccines and that's something that I think none of us wish to see happen.

And so I will end with that statement. Thank you.

MS. CHERRY: Mr. John Salamone.

MR. SALAMONE: I apologize in advance to the committee for -- in fact, I have to read my prepared statement. It's a complex subject and there are so many facets of it, so if you'll please bear with me I'll try to go through it as fast as I can.

My name is --

CHAIR FERRIERI: Excuse me.

MR. SALAMONE: Yes?

CHAIR FERRIERI: I was going to ask you to indicate your --

MR. SALAMONE: That's next.

CHAIR FERRIERI: Thank you very much.

MR. SALAMONE: My name is John Salamone. I'm president of Informed Parents Against Vaccine Associated Paralytic Polio, which is known as IPAV. IPAV is a non-profit organization representing families affected by vaccine associated paralytic polio. Our mission is to eliminate future VAPP cases through the advocacy of an all-IPV schedule in the United States and for physician/parent education.

Our goal is to go out of business as soon as possible. However, until an all-IPV program is implemented in the United States we will assume a visible and lead role in educating parents about the risk of vaccine associated polio so that they may make informed and safe decisions for their children.

We do not want what happened to our children to happen to others, especially knowing that there is a safer choice. With respect to this mission, IPAV has asked the FDA to place a black box on the oral

polio vaccine package insert.

I, as well as other IPAV families, have a very personal interest in seeing the FDA help guard the public safety by highlighting to physicians that OPV is a special case.

My son, David, is one of hundreds who have paid the price for an all-IPV policy. Make no mistake -- I'm a strong advocate of immunization and believe that we need to avail ourselves of the safest options possible in order to maintain parental confidence and universal coverage.

As an immunization advocate I am proud to serve as the vice chairman of the U.S. Department of Health and Human Services Advisory Commission on Childhood Vaccines, and in that capacity I work closely with many of you here today.

In fact, several members of this committee played an important role in changing the polio schedule from reliance on OPV to the safer IPV. The CDC accepted the Advisory Committee on Immunization Practice's recommendation for a mixed IPV/OPV schedule in order to reduce the occurrence of VAPP as a first step towards an all-IPV regimen.

The new CDC recommendation took effect in January 1997. At that time the CDC revised its polio

vaccine information sheet, outlining the risks and benefits of each vaccine so that parents could have the information available to them for discussion and true informed consent.

All of us knew that achieving health provider/parent discussion on polio vaccine options would be challenging. For one thing, most physicians had never administered anything but OPV and needed to be educated on the changes that had occurred in both polio eradication as well as the tools to control it -- particularly the enhanced IPV.

There have been significant research undertaken since the schedule change. We have found that when presented with the facts, nearly all parents opt for the safer schedule if their physicians agree. Unfortunately, habits die hard. Despite the CDC recommendation, 40 percent of children are not receiving the CDC recommended sequential schedule. And that is a best-case scenario.

Many physicians are still unaware of the rationale for this change and as a result, parents like Michelle Savalos who came here today from Florida to address you, continue to watch their children pay the price for this inertia.

I find it heartbreaking that several IPAV

families are new members, like the Savalos, whose children have contracted VAPP after -- after -- the CDC implemented its recommendations.

It's clear that more needs to be done to further alert physicians and parents to the risk of VAPP and encourage physician adherence to the new CDC recommendations of a mixed vaccine schedule.

That's why we're here to urge the FDA to require the labeling of oral polio vaccine, or OPV, and to come with a black box warning that fully outlines its risks of causing VAPP. This relatively modest step will highlight the risk of acquiring VAPP from OPV, however small.

The black box warning is the next logical step in carrying out the CDC's recommendation. It would get physicians and health care workers to break a 30-year-old habit of administering OPV alone, flagging them to stop and explain this crucial scheduled choice to their parents before immunizations take place.

If we are serious about ending polio in the United States -- and I hope we are all serious about doing so -- this is an important step to that end.

Now, before I go on I wanted to emphasize that we are not urging a black box warning for any

other vaccine or class of vaccines. We do not intend for this to set a precedent for vaccine warnings, nor should it.

The OPV vaccine constitutes a special problem because it is unique in its risk of causing polio, which it does for a reported eight to ten people a year, and for the countless numbers who go unreported.

I have to digress just slightly only because I can tell you that virtually every member of our group and their families were misdiagnosed with their polio at the beginning. So quite frankly this figure of eight to ten is only a reported figure, and obviously not a figure that I think we can say is a concrete figure.

Without a doubt, it is the duty of the FDA to act on our citizen's petition. Cases like Sierra Savalos and the others who have been VAPP since the new recommendations were made, are unacceptable and should not continue.

When the U.S. was faced with thousands of cases of wild polio VAPP was considered a "acceptable risk". It was a reality of our immunization program at the time. However, for nearly 20 years the only form of polio in this country has come exclusively

from the oral vaccine.

Certainly an unacceptable statistic given the availability of a safer and just as effective alternative. Vaccine associated polio is just as devastating to its victims as wild polio.

Thanks to the CDC a first step has been taken to eliminate this last vestige of polio in the United States. Now it is time for the FDA to take the next step in protecting our children -- a black box warning on OPV which would achieve three primary goals.

One, it would clearly state the rare but well-established risk of contracting VAPP from OPV use. Yes, this is already included in the small print on OPV prescribing information, but a black box warning would dramatically highlight this existing information, making physicians and health care providers who haven't read an insert in decades, even more aware of the risk of OPV use.

Number two, it would boldly remind physicians and health care providers that there is now a safe alternative to OPV and alert them to the new mix schedule recommendations, further encouraging them to adopt the new schedule in their own practices.

Number three, it would urge physicians and

health care providers to share this information with parents so that they can make fully informed choices about their children's immunization.

In its recommendations the CDC stressed that parental awareness of vaccine options and the importance of vaccinations is essential, and that such information should be shared so that vaccinations are carried out among persons who are fully informed.

Sadly, this was not the case with the Savalos and other VAPP families who were never made to fully understand the risk or their options.

In addition to the need to highlight the new recommendations, the fact that IPV is now widely available also makes the risk of VAPP a special and potentially avoidable problem that warrants a boxed warning for OPV.

This warning would spell out to pediatricians and other health care providers that under normal circumstances OPV is not the drug of first choice for the first two doses of the polio vaccine.

A boxed warning for OPV is supported by numerous FDA precedents that highlights significant, adverse reactions for other drug products that are not seen as first line therapies, or that should only be

used in emergencies.

Clearly, when the risk of adverse reactions, even a low risk, is severe, real, and irreversible, and when other therapies are available that don't present comparable risks to the patient, a boxed warning is appropriate.

Again, OPV represents a special case in that a safer and equally effective vaccine exists and because VAPP leads to serious disability, permanent paralysis, and even death.

Rest assured, the FDA would not be setting a precedent for other vaccines or classes of drug products. It would however, be doing its part to alert physicians who may be unaware of this CDC schedule change. This is consistent with the FDA's mission.

Objections to the black box warning for OPV can be viewed as speculative and illogical in light of the testimony we heard today. The manufacturer of OPV has stated that a boxed warning will discourage polio vaccinations. This assertion is wrong.

The boxed warning would simply take information about the risk of VAPP out of small print and remind doctors and health care providers to discuss this important subject with their parents. It

would not include such contradictions as low-grade fever and minor illnesses.

It would lead to more physicians knowing that the IPV alternative is available, which would lead to a greater acceptance of the new CDC schedule, improved parental confidence in immunization, and ultimately, greater compliance with the national immunization efforts overall.

I'm pleased to say that our immunization coverage is at the highest levels ever, which is contrary to the warning given by anti-IPV forces prior to the CDC change. This goes to show that we can do the right thing for our children in providing them with the safest possible vaccine, and not only maintain, but increase coverage.

The boxed warning is not directly intended to discourage overall use of OPV but to ensure that relative risks and benefits of OPV and IPV are fully evident to health care providers.

To indicate how incremental a step it is, I should mention again that both the CDC and ACIP view the mixed schedule as an interim recommendation before transitioning to an all-IPV schedule. I want to stress the word incremental.

We're not asking much here. But when you

watch your infant son become paralyzed for reasons no one initially could explain, when you remember him at the age of five crawling down stairs covered with bruises and falling while trying to do things other kids are trying to do, and when you watch his determination to do the things no matter how many times he stumbles, well you really want to make sure that doesn't happen to any other family, especially if it doesn't have to.

It doesn't matter that VAPP hits only a small number of people each year; it's too many. Polio has become an optional disease in America. A safe alternative to OPV exists but it is absolutely crucial that all physicians and health care providers develop the habit of informing parents of their choices.

The CDC has already done its part by making the necessary recommendations. Now we of IPAV strongly urge FDA to require a boxed warning of the oral vaccine as a next step to eradicating the needless tragedy of VAPP.

The members of this committee have within their power, the ability to make recommendations to the FDA that would finally remove all vestiges of polio in America. We implore you to do what's right

for our children. Thank you.

MS. CHERRY: Mrs. Savalos.

MS. SAVALOS: My name is Michelle Savalos and I'm here today as a member of IPAV, so is my husband, and I have a daughter named Sierra who has been (unintelligible) by vaccine associated paralytic polio.

This took place in December of 1997 after the announced change, by the Centers for Disease Control, about the need to use -- I'm going to do this because I want everyone here to know.

Again, we have a little girl and her name is Sierra, and she was born in September and she had gotten VAPP in December of '97. And this was after the announced change by the Centers for Disease Control about the need to use an injectable polio vaccine that reduced the chance of vaccine associated polio.

The fact that Sierra has contracted VAPP after the CDC policy change may seem ironic, but I find it as an ultimate failure of public policy. We weren't given the option. The physician didn't tell us our choices.

In fact, the information that the gentleman was talking about earlier, that the parents are

supposed to be receiving, we didn't even get until after the vaccination was already done with. And on top of that, it was an outdated copy -- it was a '94 issue.

Sierra is eight months old now and we love her with all of our hearts. But it breaks our hearts that she'll never be able to feed herself or sit up on her own or walk, or even hold her head up. Sierra's shoulder muscles, chest muscles, and arms are paralyzed.

Instead of learning to crawl and play with baby toys Sierra gets physical therapy four times a week -- occupational and physical. She spends 12 hours a day in splints that run from the back of her legs all the way to the tips of her toes. She also has to wear a torso brace that runs from underneath her arms all the way to her pelvic area, 16 hours a day.

And I'd like for you to know my baby book right now is pretty much bare. I don't have a first time she rolled over, or the first time she crawled, or the first time she's going to walk. When she sleeps at night she has to have an apnea monitor and also a nebulizer in case she has problems breathing.

The most painful part of this whole

situation is that it didn't have to happen; it was avoidable. And we couldn't imagine a life like this for Sierra. And you know as parents, many of you have children or grandchildren in here. You would do anything for them. And there's nothing we can do. I mean, I would die for her if I could to make her better, but that's not possible.

After Sierra was diagnosed with polio we learned that it was caused by the polio vaccine that she got when she was two month's old, and there was a safer polio vaccine that could have saved her from getting polio. But that just wasn't the case.

Since this has happened to us we have learned a great deal about what could have been. I've learned the CDC has recommended this since the beginning of October -- or January of '97. I also know that to totally eliminate VAPP that we would need an all-IPV schedule.

You know, I thought I was doing everything right for her. I thought myself a pretty educated person. I work for Merrill Lynch, you know, I read all the right books, I took my vitamins, I thought I ate all the right food, and I thought that I picked a physician -- and I'm not going to blame it all on this physician because I felt like he was a very good

physician.

I don't feel like he meant to give Sierra polio because I don't for one minute. But he did fail as a physician not to give me the information that we needed to make that choice. And it's not a choice because you don't take chances with your children. If you know that you can give your child something that's going to prevent her from getting polio and no chance at all, of course you're going to take that.

But I do -- I'm upset because the United States of America is allowing this to happen. You know, it's too late for Sierra but it's not too late for other children. My husband -- we have a million dollar cap on our insurance and we've got lifetime of promises of doctors -- she goes to an orthopedist, a neurologist, physical therapist -- in just numerous amounts.

You know, we're here today to urge the Food and Drug Administration to require black box warning and the reason we're doing it is because the doctors need to know, to be reminded that they have a duty to let the parents know.

And again I'm saying, I don't blame it all on physicians because it's beyond just the physician. I feel like it's the government and other people that

need to get involved.

There's going to be a time in Sierra's life when I have to tell her, and when I tell her -- as a child you just got sick when you were baby -- is that going to be enough? She's going to come to an age and she's going to want to know what really, really happened in detail. And I'm afraid she's going to have the same questions that I have.

Was I just a statistic? The chances are one in two-and-a-half million. Was I not important enough? If they had an alternative then why are they continuing to give oral? What do you suggest I tell her? Thank you.

MS. CHERRY: Dr. Halstead.

DR. HALSTEAD: My name is Dr. Laurel Halstead and I am a physician in the field of rehabilitation medicine. The purpose of my remarks is to support the use of a black box warning label on all polio vaccine packages.

I currently work at the National Rehabilitation Hospital here in Washington, D.C. where I am the medical director of the spinal cord injury program and director of the post-polio program.

Although I have been a practicing physician for over 30 years I have no special expertise in the

area of vaccines, immunology, or virology. However, I do have special expertise and knowledge with paralytic poliomyelitis, from both personal and professional experience.

I contracted a severe case of paralytic polio at the age of 18 in 1954, which required several weeks in an iron lung, six months in a wheelchair, and one year in a shore leg brace.

Despite a generally good recovery my right arm has remained paralyzed for the past 44 years. My overall neurologic status remained stable until the mid-1980s when I began experiencing the onset of a new, progressive weakness in my legs and left arm, intense fatigue and muscle pain, which we now recognize as post-polio syndrome -- a long-term sequelae of polio that affects 40 percent or more of the 600,000 polio survivors.

I am here today representing these 600,000 survivors and I can guarantee that not one of them wants to see a single additional American contract polio. My own polio occurred of course, before a vaccine was available to the general public. For me and for hundreds of thousands of other Americans, paralytic polio was an unavoidable hazard of growing up in the pre-Salk and pre-Sabin era.

That of course, has now completely changed and polio is, if we want it to be, now 100 percent preventable. Which raises a number of interesting questions.

If another vaccine caused the disease it was meant to prevent, would anyone stand by and let it happen? Why does polio have this unique status that we grant it alone? Immunity to be given by healers in a kind of Russian roulette so that eight to ten, or whatever the number is, of children a year will be paralyzed. Isn't just one more lifetime of paralysis enough?

What if rubella vaccine caused German measles in only a handful of cases of birth defects and mental retardation here? Would we use it? Would the public accept it? What if the smallpox vaccine were still necessary and caused an occasional case of deadly or deforming smallpox? Would you want your child to have that vaccine?

What if a newly discovered AIDS vaccine caused ten cases of AIDS a year? Would you want that vaccine for yourself? Why is possible death or a life of paralysis from a polio vaccine an acceptable option?

I urge this committee to take the strongest

possible stand to implement the CDC recommendations for sequential, IPV/OPV schedule and to include a black box warning so all polio will one day be eliminated from this country. Thank you.

MS. CHERRY: Dr. Levengood.

DR. LEVENGOOD: Hi, I'm John Levengood, director of the Epidemiology and Surveillance Division of the National Immunization Program at the Centers for Disease Control and Prevention.

I'm here today to represent the position of the National Immunization Program about a boxed warning on the labeling for oral polio vaccine -- called OPV from here on.

Vaccine associated paralytic poliomyelitis, or VAPP, is a rare but severe adverse event undisputedly caused by OPV. The prevention of VAPP was the main justification for the recent change in policy of the ACIP and CDC to recommend a sequential schedule of two doses of IPV followed by two doses of OPV for polio vaccination in the United States.

Although all IPV and all OPV schedules remained acceptable parent or provider options, the sequential schedule is the preferred choice. With further progress and global polio eradication we will undoubtedly consider changing the preferred schedule

to all-IPV for several years before ceasing all polio vaccinations, thus eliminating the problem of VAPP.

It is very important that parents and providers clearly understand the risks and benefits of immunization. CDC supports complete, accurate, and well-balanced labeling, and educational efforts to empower parents and providers to make informed choices.

To this end CDC conducts numerous training and education sessions, including presentations at National Provider Organization meetings, as well as interactive satellite courses targeting tens of thousands of immunization service providers throughout the United States.

Further, a variety of surveys have consistently shown that recommendations of professional organizations such as the Committee on Infectious Diseases of the Academy of Pediatrics, published in the Red Book, and the recommendations of the Advisory Committee on Immunization Practices of CDC, consistently rank at the top of ways in which practitioners report learning about immunization policy.

For example, even though the recommendation for sequential schedule was not formally issued until

January 1997, data on net doses of vaccine distributed have shown a marked increase in IPV use. In 1996, 1.28 million net doses of IPV were distributed in the United States, compared to 5.23 million doses in 1997.

Further, the proportion of all polio vaccine doses that are IPV rose from six percent to 29 percent in 1997. Therefore, we believe our current methods for communicating to providers is getting the message out.

Additionally, under the National Childhood Vaccine Injury Act of 1986, the CDC is required to produce and distribute vaccine information statements -- or VIS -- for each vaccine, such as polio vaccine which are included in the Vaccine Injury Compensation Program.

The law was enacted to ensure that the benefits and risks of vaccines were presented in a clear and factual manual. Each VIS is produced in consultation with parent and provider groups and is tested for understandability. Some states provide these statements in several different languages.

Because the law requires that the providers give this information to every parent or guardian prior to vaccination, we consider this a powerful means to educate them about the risks and benefits of

each vaccine.

I provided the committee copies of the current VIS on polio and I have several other copies on the table outside, although many of you here in the audience have worked with us in developing this particular statement.

On this you will see information about the various risks and benefits of the three polio immunization schedules: all-IPV, all-OPV, and the preferred choice -- the sequential schedule.

Nearly all vaccines -- tetanus toxoid being a major exception -- had benefits both to individuals and to society, in contrast to many drugs. This places vaccines in a somewhat different position than the pharmaceuticals that were discussed earlier.

Just this year, CDC announced the results to-date of the Childhood Immunization Initiative begun during the early 1990s. During united infrastructure of public and private sector partnerships, record national immunization coverage rates of 90 percent or more were achieved for most of the individual immunizations needed by the time a child was two years old.

What that translates to is a record low incidence of vaccine preventable diseases and deaths

among children nationwide. We can envision a scenario where over-emphasis on a very low vaccine risk might be inappropriately highlighted and cause under- or non-use of a vaccine when there is no alternative vaccine available, leaving the public vulnerable for serious disease outbreaks.

Vaccines are extremely safe, but not perfectly so. We would like to go on record as voicing a concern about the precedent setting concept of placing boxed warnings on vaccines.

A warning focused only on risks without concomitant discussion of the benefits of vaccination could be associated with other warning labels that the public sees, which are specifically designed to deter use -- such as cigarette and alcohol package warnings -- and some that do not use message to providers and other.

In our opinion, the need for highlighting the minimal risks associated with the vaccine out of context with the much larger benefits, is not scientifically justified. It repeats information already contained analytically and distributed widely by CDC in recent information statements.

And lastly, it might set a dangerous precedent affecting use and acceptance of vaccines in

general. Thank you very much.

MS. CHERRY: Miriam O'Day.

MS. O'DAY: Good afternoon. My name is Miriam O'Day. I'm vice president of the Immune Deficiency Foundation. The Immune Deficiency Foundation furthers education and research into the primary immunodeficiency diseases. The IDF is a national organization dedicated to improving the lives of some 40,000 individuals affected with primary immunodeficiencies in the United States. IDF works closely with IPAV and supports their efforts.

Primary immunodeficiencies are a group of nearly 70 different disorders. Most patients present clinically with an increased susceptibility to infection. These infections can be chronic or unremitting, and unusually severe.

Now, as a group, primary immunodeficiencies are more common than both childhood leukemia and lymphoma together. I'm here today to endorse the use of a black boxed warning label listing the potential adverse side effects of the oral, live polio vaccine. I'd like to elaborate further on the reason Immune Deficiency Foundation supports this initiative.

In September of 1996 the Centers for Disease Control and Prevention, CDC, accepted its advisory

panel's recommendation to change the routine, childhood polio vaccination schedule to decrease the occurrences of vaccine associated paralytic polio, VAPP.

The CDC now recommends that U.S. children receive two doses of injectable polio vaccine, killed virus IPV, followed by two doses of oral polio vaccine, OPV, live virus.

Previously, the common polio vaccine protocol consisted of an all-OPV schedule. The Immune Deficiency Foundation has endorsed and continues to support this recommendation, and we'd also like to note that households with immune-deficient persons that have children that are being vaccinated, have them vaccinated with IPV because the live, oral polio virus is excreted in the stool and may pose a risk to individuals with a compromised immune system.

I mention that because the Immune Deficiency Foundation, in cooperation with the CDC and Johns Hopkins University, is currently conducting a study to determine the amount of live vaccine that may be present in current stool samples of immune deficient patients.

The objective of the study is to determine if some immunocompromised patients who received the

oral, live polio vaccine as children but did not develop VAPP, may still carry the live polio virus.

The U.S., as you heard today, has been free of the wild polio virus since 1979. The only remaining cases of polio in the U.S. since 1979 are associated with the live virus in the oral polio vaccine.

Infants with primary immunodeficiency diseases are at a significant risk for vaccine associated paralytic polio. IDF is concerned that if the sequential schedule is not followed, OPV may be administered too early.

It's also very important to take into account the age at which most patients with primary immunodeficiency disease are diagnosed. In most cases the diagnosis is later than the first six months of life, and in many cases, is not made until age one or older.

And in addition, 70 percent of patients surveyed in a nationwide survey by IDF have no known family history of primary immunodeficiency disease. Furthermore, the OPV prescribing information does not provide for administration of the third dose before 12 months, although this is a common practice among pediatricians.

The use of a black boxed warning which is heeded by physicians, would allow these children the opportunity to be diagnosed before a vaccine associated injury. We could eliminate the needless risk from the oral vaccine during the 2- and 4-month series of immunizations.

The goal of adding inactivated polio vaccine to the accepted schedule was to minimize the number of cases of VAPP, many of which occur in babies with primary immune deficiency.

We believe it would be prudent for this advisory committee to support the black boxed warning on the live, oral polio vaccine. The boxed warning is necessary to advise physicians and parents.

The National Immunization Program continues its public service campaign aimed at educating parents and pediatricians regarding the advantages of IPV in the first year of life. Parents are urged to understand these differences allowing for an informed decision which best suits their children.

However, physician education remains a key element in the total health care decisions, and a black boxed warning will assist many physicians with awareness of an issue they may have previously ignored.

I would encourage this Advisory Committee to support the black boxed warning on the oral live polio vaccine. Thank you.

MS. CHERRY: Is there anyone else in the audience that wishes to make a statement at this time? This is the final opportunity. If not, then we'll go on with the meeting.

CHAIR FERRIERI: Thank you, Mrs. Cherry. I want to thank everyone who came and presented today. This was very helpful for the committee. We are interested in always hearing all sides of an issue.

I'd like to open our discussion by reminding the members of the committee who remain, of the specific issues that FDA CBER has addressed to us so that we confine our discussion to these points and stay targeted, so that we don't overuse the time of all the individuals who are here.

So I would entertain anyone who would like to open this up in a general way, and specifically in addressing what perhaps, is a start. How they view the current sections of the package insert, the adequacy of that. And then lead into the possible utility of a boxed warning.

Dr. Snider.

DR. SNIDER: Well, several things. First of

all, I would like to remind everyone why we got into this transition or this interim schedule instead of going straight to an IPV schedule.

And that has to do with the fact that it is believed that there are still a large number of importations of wild polio virus into the United States. We can't quantitate that. Fortunately, we don't have cases caused by wild polio virus.

The question is, how much the mucosal immunity induced by OPV might be contributing to the fact that we are not seeing these wild polio cases. And so that's the reason that -- there's still, from the experts, still some question about what contribution OPV is making to the entire population and the fact that we're not seeing wild type polio in the United States.

And concern that if we went to an all-IPV we might exchange VAPP cases for wild type polio cases, and even in increased numbers. But nevertheless, I think we all have the same goal in that we would like to go to an all-IPV and then to not having to vaccinate against polio at all because we have totally eliminated polio.

With regard to the specific issue of trying to prevent vaccine associated polio cases, it seems to

me that we've heard information presented today that suggests, as if always the case, when a new recommendation is made or a new innovation comes about, that there's not rapid adoption of a new recommendation or a new treatment, and so forth.

And so it seems to me the question is, how can we speed up the adoption of the preferred schedule, and how can we speed up making sure that parents and providers are aware of the options and make informed decisions?

And the question is whether the boxed warning is the best way to go or whether there are other actions that should be taken, and whether the boxed warning would make any contribution to that?

It's not at all clear to me -- I don't know if FDA has information -- about what happens when boxed warnings are put on products; whether that changes physician practices or not. But that would be a key question, I think.

Because I can think of a number of other ways that one might get the information out that might be more or less effective than the proposed solution. With regard to the information that's available, one can debate how much you should say and how you should say it, but it seems to me that the information is

there in the critical documents -- namely the package insert, in the vaccine information sheet, in the ACIP recommendations, and in the AAP recommendations.

So the information is there. The question is, how to get people to act on it.

CHAIR FERRIERI: Dr. Daum, would you like to contribute to this, as a former member maybe, of the Red Book or current member?

DR. DAUM: Yes, I guess you're going to hear thoughts that haven't been totally edited or a conclusion definitely reached. But I guess I want to begin by particularly telling the parents who came before us today and to other parents who I've talked with before in the past, my compassion goes out to them.

I mean, I hear stories like this and I find them wrenching and emotional and I'm a father also, and believe me my heart was with you when you spoke.

We bring vaccines to the table and are strong advocates of vaccines in the belief that, like any medical intervention it has risks but that these risks are outweighed -- and in this case dramatically outweighed -- by the benefits.

Before the introduction of polio vaccine there were approximately 50,000 children a year

paralyzed in this country. And at that time if anyone said we have an intervention which may change that number from 50,000 to six or eight or ten, or whatever the right number is, anyone would have signed up for it and said, well we'll take that tradeoff.

And now we've come around to the full circle where we've been so successful with our program that that kind of side effect if you will, is no longer acceptable to us. And so the CDC and the WHO and other organizations have moved, in I think a very dramatic way, in the last five or ten years, to decrease polio throughout the world.

I'm absolutely stunned by the progress that's been made as we move closer and closer to the point where the virus is eradicated from all human beings and as Dr. Snider pointed out, we will no longer have the need -- I think someday in our youthful lifetimes -- to immunize anyone.

So as we move toward that day what's the best way to proceed? And everybody in this room knows that the debate has been acrimonious and long and risks and benefits have been weighed very carefully and very reasonable people have come to slightly different conclusions about how to do this and how to phase this program in.

But nobody disputes the fact that the oral polio vaccine on which we've made such incredible progress in this country, also has problems and may now, as a primary and sole means of immunizing children against polio, have to some extent, come down more on the risk side than the benefit side.

So the question is, as Dr. Snider pointed out, how to tell this to people. I think that there's been an awful lot of communication of this kind of thing. It's been in a lot of magazines and lay magazines, it's been in newspapers, it's been on television. There are information sheets about it.

Three or four separate, so-called august bodies have spoken about preferences for it. And yet somehow obviously the information isn't out there for everybody to know.

Does a boxed warning accomplish that goal? And what's the sort of risk and benefit of putting a boxed warning on this product? Well, there's lots of medical interventions in this world and there's lots of dangers in this world, and we can't sort of boxed warning all of them.

I think we have to communicate as best we can to the people who are at risk, what the risks and benefits are and hope that knowledge and common sense

will carry the day.

And so I guess I'm concerned that as Dr. Snider I think, sort of said, that the information's out there. It's not that anyone's pretending this isn't the problem, it's not that anyone doesn't have compassion for people that experienced this horrible complication.

And yet I'm not -- I guess I have some real concerns in my mind that a boxed warning is going to take us further down the road of informing people about what's going on.

I'm also very worried that -- it seems logical to me that if a boxed warning were to be applied to this that we ought to begin considering literally thousands of other things that are dangerous -- about medical interventions and other things that should also be box warning.

And so I'm not enthusiastic about this particular approach, but I am very concerned about making sure everybody who's immunized with OPV be fully informed and fully aware of what the possible hazards might be.

CHAIR FERRIERI: Thank you, Bob. That was very eloquent. Kathy -- Dr. Edwards.

DR. EDWARDS: Well certainly, I participated

in the last IOM discussion and was very moved by what you, as parents, said at that time, as I currently am. And obviously, you know, we are very sorry and certainly don't want this to happen to any other children.

I think one of the concerns I have is that as a physician I rarely ever read what's in the box, and maybe that's not something I should say. But I think also, if you go to a vaccine clinic and you watch busy nurses, you know, giving vaccines, they quickly go through the boxes and the packages and throw them very quickly into the wastebasket.

So I really think we need to educate people, and certainly I spend a lot of my time doing just that -- giving talks about this issue. But I don't think that many of us -- and certainly I think that scarcely any parents get the package insert at the time the vaccines are given.

So I think we do need to come up with a better way to tell people about this problem, but I really worry that it isn't this forum because so few people actually read the labels at this particular time when they're in the clinic.

So that I don't think that it's going to solve this issue in a practical way, and certainly I

think that it's going to take some other method to do it other than just the boxed warning.

CHAIR FERRIERI: Thank you, Kathy. I would echo her lack of confidence in physicians reading package inserts. I'm sorry to disappoint those of you who think we do. We may do it at some point but not consistently and not with every product. And so we're relying on these other mechanisms to educate -- to other health care providers to actually give the injections as well as to parents.

Dr. Snider.

DR. SNIDER: I had one question for the FDA folks, or the manufacturer. I think one of the things I would hope we all would not want to happen is that we would send a message to India or sub-Saharan Africa, that for them they should give up on oral polio vaccine and try to use IPV. It would be a total disaster. We would not be able to achieve -- I don't think -- polio eradication. I mean, it's iffy enough with OPV.

And if somehow we send a message that OPV is a second-class or a very dangerous product that they shouldn't be using, then lots of people could be harmed and I think -- I want to think about the world as a global community and unfortunately, although we

like decisions to be simple, they're very complex, and this is one of the complexities.

So my question is, if the FDA were to put a boxed warning on OPV for the U.S., would that -- I mean, I'm sure the media might pick it up -- but would it also have to appear if it was produced in the United States, in inserts that would go to these developing countries?

CHAIR FERRIERI: Dr. Baylor, would you like to address that point? Or Dr. Zoon.

DR. ZOON: Yes, Dr. Zoon. The answer is yes for that company. If that's their product they would have to include all the important information in the labeling.

CHAIR FERRIERI: So there's uniformity regardless of the site to which the product is distributed then, Dr. Zoon? Is that what you're saying? So that we can't have selective --

DR. ZOON: Right. For U.S. licensed products, that information has to be there, whether it's in the U.S. or abroad.

CHAIR FERRIERI: Thank you.

MR. JOHN SALAMONE: Madam Chair, I'm sorry. I know it's beyond the public comment period. Is it possible for me to say something?

CHAIR FERRIERI: Yes. Please come up to the microphone then. Announce your name again so the transcriber will -- it's working.

MR. JOHN SALAMONE: I'm sorry, it's John Salamone again, Informed Parents Against VAPP. I just find the argument so incredible I can't stay in my seat.

To actually think that in Third World countries people are going to be lined up for their vaccinations and say, well wait, I heard this news story, or I heard about this package insert that you know, says that you know, there's a chance that we could get polio from that oral vaccine you're giving us.

People out in the field will tell you that that's a ludicrous comment. To think that people are going to reject this vaccine in those Third World countries because in the United States a reasonable boxed warning label would be put on it that is already contained in the small print.

The other thing that concerns me is, first I hear from representatives of Lederle and others about how -- well listen, if you get a black boxed warning label on there it's going to scare people to death; people aren't going to get their vaccinations.

Then I hear from doctors here who say, well listen, nobody reads that stuff. Well, we can't have it both ways. It's either going to scare them or they're not reading it at all. I just feel like I have to make that distinction.

And also make it clear that with the case of polio we're talking about something very unique and different -- a special circumstance. You have a situation where you have two vaccines: one that in the United States for the purpose of protection of that child is just as effective as OPV.

The only difference is there's zero chance that child could contract polio from that vaccine. And we keep talking about it as if this is such a precedent.

But this is a situation where you have a choice of two vaccines: one which by the very admission of the CDC, is one that they recommend to start with and ultimately would just as soon everyone have for all four of their vaccinations.

I'm sorry. I just had to make that point.

CHAIR FERRIERI: Thank you. Yes, Mrs. Rovner. Please go ahead.

MS. ROVNER: I'm sorry. I don't really understand how the oral vaccine affects the wild

vaccine. I understand that it helps control it, but I'm not sure I understand why. Could you explain that just very briefly to me?

DR. SNIDER: Well, I'll try. I'm not a polio vaccine expert. But the point is that when you ingest a vaccine you have an immune response inside the intestine. When it's injected the immune response inside the intestine is much lower, or non-existent.

The immune response in the intestine is important in that it protects an individual from transmitting it to other people. I'm just brainstorming about some other side effects that may occur.

And I think, you know, John raised some very valid points. But again, I think we need to think about some of the other implications of the box warning. Again, I think we have the same objective; the question is really how to get there.

Another question I have that related to Norm's presentation is, what would be the implications of the boxed warning for general encouragement to get immunizations? I mean, how far does the boxed warning have to go? Does it -- is it only attached to an encouragement to get this product or if there is a general encouragement to get polio vaccine do you have

to say something about it?

I'm just not sure how far -- I'd like some clarification on how far you have to go attaching the boxed warning to more generic statements about immunizations.

DR. BAYLOR: I can answer that, Pat.

CHAIR FERRIERI: Please.

DR. BAYLOR: Generally the boxed warning is not for -- it doesn't talk about options, it talks about -- it emphasizes contraindications and adverse events. The boxed warning would not say there's an option, i.e., IPV instead of OPV, and the boxed warning that was presented to us in the citizen's petition as I presented on the slide, it didn't have anything -- it didn't contain anything such as that, and it generally doesn't contain anything about an additional product.

But one thing, in the package insert -- and this is rather unique for vaccine package inserts in general -- but both of the licensed polio vaccines -- the oral polio as well as the IPV -- mention the alternative schedule, the sequential scheduling.

So here we have a product such as OPV and you actually mention your competitor's product in that package insert. So we require that both of those

package inserts contain information on the sequential scheduling.

DR. SNIDER: But as far -- while you're close to the microphone -- as far as advertising, you are talking about here, materials that would be developed by the manufacturer of the product --

DR. BAYLOR: Yes, yes --

DR. SNIDER: You're not --

DR. BAYLOR: -- not the government.

DR. SNIDER: -- talking about materials developed by various groups like CDC or AAP that would be developing general vaccine materials --

DR. BAYLOR: That's correct.

DR. SNIDER: -- that might happen to mention the specific vaccines?

DR. BAYLOR: That's correct. It would be limited to the manufacturer. And if I'm mistaken, we do have our promotional person here.

CHAIR FERRIERI: Did we answer the question, Ms. Rovner?

MS. ROVNER: No.

CHAIR FERRIERI: I didn't think so. Could you please state it again, though? Could you state your question again?

MS. ROVNER: Okay. I want to know how the

oral vaccine protects the community against the wild virus. That's what I'm trying to --

DR. SNIDER: All right. I'm sorry. From the standpoint of the oral vaccine, you heard people mention that the oral vaccine is transmitted in the stool to other people. And if you had 100 percent of the population being immunized, then it wouldn't make any difference.

But the fact is that we never have 100 percent of the population immunized, you know, going in to get immunization. So what happens is because the oral vaccine after it's ingested, does get excreted, it gets transmitted into the community so that some people presumably, get immunized who didn't go in for an immunization in the clinic.

MS. ROVNER: In other words, it gets to people before the wild type --

DR. SNIDER: And unfortunately some of them as you saw, get vaccine associated paralytic polio, however. So it's a double-edged sword there in terms of the transmission: potentially protection of additional people from polio who never got their immunization, but some recipients who get it passively also wind up getting vaccine associated paralytic polio.

CHAIR FERRIERI: It's been viewed as tremendously important worldwide in underdeveloped countries in bringing up a level of immunity and having the great ease of administration as well, more affordable, easily dispensed, not requiring the same equipment that you would need for injection. So it has great merit still, worldwide.

Dr. Eickhoff and then Dr. Evans.

DR. EICKHOFF: I certainly share many of the thoughts that have been expressed on the other side of the table, particularly with regard to compassion and sympathy for the children and their parents who have become victims of vaccine associated paralytic polio in the recent past.

I think the issue before us is really one of -- well, obviously public education -- but I'm going to focus on provider education at the moment. The history of major shifts in vaccine policy in the United States suggests that it takes, you know, usually some years and sometimes as many as five or ten years, to bring about a high level of compliance, if you will, among physicians and other providers.

For example, the adoption of universal immunization with hepatitis B using hepatitis B vaccine took, oh several -- at least several years and

maybe longer -- to bring about. And I think while it's much, much better in recent years it still has a little ways to go.

Universal use of varicella vaccine still has a long way to go. So it's one of -- the issue is certainly one of continuing focus on provider education and I think that's the major challenge here.

I don't think any of us around the table and I don't think it was realistic for anyone who believed that physicians would totally fall in line with the change in IPV/OPV policy in January of 1997 when it was first announced by CDC.

I was really encouraged by what Dr. Levengood said about the rather sharp rise in utilization of IPV during 1997, and would really look forward to another sharp rise in 1998.

But the fact remains I think, that the habits of physicians who have been using OPV for 20 years are sometimes very difficult to change. And I think the focus has got to remain on provider education.

So I would certainly strongly encourage the members of IPAV and the Immune Deficiency Foundation to do all they can to focus on provider education with regard to this change in vaccine policy.

CHAIR FERRIERI: Dr. Evans.

DR. EVANS: Actually, I bring a couple of different interests to being on the committee today. Being with the compensation program for the past eight years we have been in the unique position of seeing firsthand through records, the kinds of results that can happen when a baby or an older child or an adult has vaccine associated paralytic polio. And I remember one year we had three cases in which there were ventilator-dependent infants -- that's how severely affected they were.

And of course, these parents, some of whom have come to our commission and have spoken and we have a member on our commission, John Salamone. So this issue has been something that we're very familiar with and my heart does go out to the families that have encountered this.

It seems to me when I considered this as an issue about putting the boxed label in, my first reaction was, is that really the issue, or is the issue how well are we informing providers and how well are providers informing patients?

And with polio we have a known adverse event, we have data, we have a marker, and we have this unique requirement that every time a covered

vaccine is given -- and now there are ten vaccines that need to have information statements -- every time a vaccine is given by law, they should be given to the parent or legal guardian.

And at the same time the vaccine information statement is not designed to replace communication; it is there to facilitate. So I guess one of the questions I had when I first heard about this effort is, what data are there that show how frequently physicians, providers -- whether it's FPs, pediatricians, whatever -- are utilizing these information statements?

And beyond the basic question, how much are they aware of the recommendations themselves? I'm not aware of any information that really tells us much about that. And so I guess my reaction to hit listing this is, I want to know more about that and I want to make sure that we redouble our efforts to make sure that providers are aware of the importance.

Because I remember when I was giving OPV it was something, one in a million. That was something very obscure, something very hard to get a hold of. But now that I've become much more familiar with this issue, I mean, part of the process it seems to me we have to find ways to make sure that this information

it gets out there.

CHAIR FERRIERI: Thank you. Dr. Karzon.

DR. KARZON: I have a special relationship with polio. I hate it. It's an awful disease. And I'll tell you why I feel this way. When I was a young physician in training, and I trained in pediatrics and then infectious diseases, and part of my training was a year in an infectious disease hospital.

And during the polio season we had several hundred cases, and I was a senior resident taking care of them. And many a night I slept there, literally surrounded by tanks, breathing for the kids and young adults. And I'd go over and clear out their trachea so they can breathe. I hate it. It's an awesome disease.

And then I worked later on as part of the Salk vaccine development program. They used the first Salk vaccine, and then later on actually the Sabin vaccine.

The world has changed and I'm very grateful. So now what do I think we should do about the boxes? Well, I don't think putting anything in the box is going to change mothers and baby caretakers in their choice of material for vaccine because there are now three, rather complex choices.

Even understanding them is difficult, what they each mean. I see the defect as a defect in the providers -- I hate that word -- the physicians and the nurses who give out vaccines and who are responsible for pediatric care or a generalist who takes care of children and adults in the clinics, including public clinics that immunize children.

If they are not making very plain what the options are and what they mean, that is a defect. That is the defect. Nothing else is the defect.

Now, how do we go about making certain that this information is handed off to the mothers who come in for immunizations? How do we make sure that that option is presented to them so they can make a knowledgeable choice? Because it might require some explanation and answering questions, and that all takes time.

But we must do that. That's part of the business of the physician or physician's office, or a clinic. If we're not doing that let's do it. Now, how do we get this information out to those people? And this has been said before this afternoon, but I think maybe we are learning that we are not doing as well as we had thought.

I would have thought that there's no

pediatrician I can imagine who doesn't know these facts. I find it incredible, but obviously there are some and maybe the important thing is, they don't tell the parent what their options are and the significance of it.

I think our goal is to have every person who can possibly understand it in any language, to know their options and the significances. It's the only fair thing because the stakes are high. Even though the statistics are infinitesimal to think about, one in a million is a low number. But they still have to have the information to make their decision.

The schedule is unusually complex for a lay person. Inactivated vaccine, live polio at the end of two shots, and so on, has to have an explanation. I think we have to go back to our organizations that we represent or can influence, and make sure that this information is out and used. And then survey it and check and see if it's used.

It's that important. If we are going to ask people to take the preferred schedule they have to know: is the risk reduced; how much; what can we expect; why are you asking this? Those questions have to be made public.

Every child should be immunized. Every

schedule works. There are reasons why -- and I think sound epidemiological reasons, not personal reasons -- why having a population that is largely in a position of having elementary enteric immunity is valuable.

Introduction in the United States is a real possibility. It has occurred -- not very recently but since the vaccine's available. It's a real possibility as long as there is polio in the world, if we don't get a very high immunization rate of one those three sorts, we're going to get polio again.

And we, the United States, has had a leadership position in helping to eradicate polio in the world, and that is a wonderful thing to do. I don't care who the little baby is, but if he happens to be in Africa I don't want him to get polio too, and we should all feel that way and we're doing it.

But in the process and until we get the world disease-free -- and I agree with those who say we're going to do that because it is a disease that can be eradicated -- that's the first order of business. And that's a lot of people. Again, we've got to make sure that nobody in the United States gets polio inadvertently and that everybody has that option.

Some people know more than I about

dissemination of information and education and also checking to see that it works, and those people should go to work to make it work.

About boxes -- I really think that's not an advantage to put in the box because I don't think that's going to move physicians or nurses or clinics to do anything differently. It's going to be there. It's in the same wrapper. It's right there in a different paragraph.

If you want to know what adverse reactions are they're listed. And a doctor who doesn't pick that up won't pick it up in the box. Boxes are generally used for chemical drugs where you have other options and you warned off once and you go to another one. There's no option in vaccines.

And I don't know that boxes are the answer. We have the same problem with coverage, with whooping cough, diphtheria -- deadly diseases, particularly. And we have the same problem of education of care givers. That's the sound approach.

I'll say it again -- I don't believe putting this in a box is going to help unless we do everything else. Unfortunately. It's sort of strange, the concept of a box has been the central point in those who want to prevent polio in children. It's a funny

thing to put your hands on as a solution, because I don't think it's useful.

CHAIR FERRIERI: I'd like to call on Mrs. Cole who's been very patiently waiting, and then again, to Mrs. Rovner. Rebecca.

MS. COLE: Well, I agree totally with Dr. Karzon. I think that one of the major issues is public awareness, but the box on the package insert is not going to do it.

You could put a box on every vaccine for every potential, adverse effect. Some kill even more than are injured by polio vaccine every year. We could do that and we'd end up as they say, desensitized. The boxes would no longer mean anything because that's all that would be on the papers.

I know from personal experience there are many, many doctors and nurses out there that do not read the literature and that do not discuss anything with parents. I've known mothers who come to me and say, I asked my doctor about this and he said, you read too much. Or, you watch too much TV.

As far as I'm concerned, that is as egotistical and cocky as a person can get. Because every human being in this country has the right to know every risk, every potential side effect, every

single thing -- every choice about everything they put into their bodies.

It's a right. But people don't afford them that right. Many times it's our health care providers.

You all have done a tremendous job. When I saw that the recommendation now is two shots and two drops, I was just amazed. That's a major advancement. You've done a wonderful thing so far, but I don't think the box, the black box, is going to do anything more.

I think efforts to promote more public education would be more productive at this point.

CHAIR FERRIERI: Thank you, Rebecca. Ms. Rovner.

MS. ROVNER: I couldn't disagree more. I'm not a medical person; I'm a communicator. And just the mere presence of a black box on anything is going to get more attention from the media, from educational places. Then maybe if not a single health provider ever reads what's in the box the box is going to covered and everybody is going to know the box is there.

And if a parent comes in with a child to get a shot and says, I know there's a box; what does it

say? That might save a child. I grew up in the polio era. My kids were born just in time to get the vaccine. I have relatives who had polio -- who have polio.

And I think it is unique, and I think it's one of the most exciting medical advances in my lifetime and I'm, as I say, not a medical person at all.

You talk in vague terms about educational and public awareness, but that is not the purview of this committee as I understand it. A box is. That's my feeling.

MS. COLE: Pat.

CHAIR FERRIERI: We have a rejoinder here from Rebecca.

MS. COLE: I did not make this a point a little while ago. My oldest son died ten years ago because of the lack of information about corticosteroids and the potential danger with chicken pox and measles.

I was instrumental in getting a warning put on labels on all corticosteroids in this country by the FDA. More children were dying -- more immunosuppressed individuals were dying every year of chickenpox than the individuals that are damaged by

polio vaccine every year.

My point was, the warnings on corticosteroids are there. What can be done to possibly save people are there should this side effect occur. That won't happen with the black box.

That box is going to be there -- I think the FDA said that there is no option listing in the black box. Is that correct? It's just a warning. It's just a, this can happen. There are many other things out there that are just as dangerous or just as -- maybe even more potentially fatal than polio vaccine is.

And they are not all in black boxes. I'm not disputing the fact that would get attention -- it really would. But there are other things that could be considered black box material as well. Do we add all of that?

MS. ROVNER: Well, you have to take it case-by-case.

MS. COLE: How many have we got? How many people die from hemorrhaging from aspirin use every year?

CHAIR FERRIERI: Dr. Evans, you had your hand up or not? Okay. Dr. Hall.

DR. HALL: There's very little I can add to

anything that has been said, except that one little piece of information comes from a current study that we are doing in our area about the use of polio vaccine by our providers -- if I may use that word -- in our area.

And this is actually done with a couple of residents at our university. And it's a fairly large, just survey study. But from that we can at least thus far note that there isn't a single provider who is not -- in this particular group at least -- who is not aware of the dangers of polio vaccine.

Also there is not one who is not aware that there are choices to be made among the schedules. And beyond that -- and they also, with almost complete compliance here -- they realize at least, that this information should be presented to the patient.

However -- and these methods of trying to assess whether that gets to the patient, is very difficult. We don't really know. So all I can add to this is to say that -- to verify again from what little information we have, that the information is out there -- the providers and all are aware -- and how well aware they are making their patients is individualized in various offices.

And again, I don't know how one can best

make that happen. And also we've learned that most patients will follow whatever their doctor recommends, and that that is actually the most important finding.

So somehow I don't think that the black box is going to -- that warns the box, whatever -- is going to help in that problem. And I don't know what the best way is, but I think if our time and resources could be utilized best it would be toward that, of trying to get that communication between to the parents.

CHAIR FERRIERI: Thank you, Caroline. I think Dr. Baylor, you heard that with an exception at the table, Ms. Rovner, there is no sentiment for having a special box in the package insert for oral polio vaccine. And it doesn't appear that anyone believes that this is going to accomplish what the goals would be and further communication.

Other options that we could develop hopefully through FDA, might improve the dissemination of what is available to all physicians, nurses, other health care providers. But for the sake of discussion I'd like input from the committee on, if we were going to write a box warning, what possible, scientific criteria would lead you in that direction?

We know that for adriamycin it becomes very

evident what the demand would be there to have it, and some other drugs with extreme toxicity. But what scientific criteria would have led you in the direction of writing a box, special box warning for polio -- for oral polio vaccine? Bob?

DR. DAUM: I'm going to have to think about that, Pat. I wasn't prepared for that question.

CHAIR FERRIERI: No, none of us was, but I think you would have to imagine that the magnitude of the risk would be extreme; that the risk of acquiring a particular disease is so great that you're willing to take on whatever the risks of the product might be; that there was a higher risk, not the risk that we currently know of; dissemination to others; or that the risk is greater to the recipient of the oral polio vaccine.

These are the avenues that would lead me in support of a boxed warning, Norman. Do you have any thoughts, Dr. Karzon, about scientific criteria that might lead you to create a boxed warning for oral polio? What would be the imperatives that would require us to move in that direction? Ted.

DR. EICKHOFF: You mean, given what we currently know about oral polio vaccine?

CHAIR FERRIERI: What scientific criteria --

this is the question that FDA CBER would like us to address -- possible scientific criteria for determining whether the box label. So I've enumerated at least two.

Norman, do you want to seek further clarification on this or do you feel we've come as far as we can?

DR. BAYLOR: I know that's a very difficult question and that's one that we've been struggling with also. I think the advice that's been given to the FDA so far has been very useful and perhaps we can close it here. I mean, we may seek your individual advice at some point just in passing.

But it's a very difficult question, not just for vaccine associated paralytic polio but for any vaccine. What type of criteria do you set up to make that decision? I think it's been very useful, the two examples that you've given.

CHAIR FERRIERI: I would like to respond to Mr. Salamone in terms of, we can't have it both ways. We didn't write any document that was submitted by manufacturers. That was new to us and we wouldn't have written it that way.

Those aren't compelling reasons for me not to want a boxed label. I'm not convinced that it's

going to lead to less compliance.

So I affirm what Dr. Edwards said and that is, that the average health care provider receives a lot of this information through other channels -- the media, scientific writings, and so on -- but not primarily through package inserts. Although they are extremely valuable and we do refer to them when specific questions may come up.

But I think that it won't serve the purpose that we would like to achieve and we share your goals and certainly would love to never have another case of VAPP occur. But I don't think that the box warning is that direction.

So there are any number of scientific criteria that would have convinced us. I mean, if you had a high risk of a hematologic abnormality following the vaccine -- any number of things that relate to the therapeutics and the labels that are used for a number of products that are viewed as "dangerous" -- highly dangerous. And when used by inappropriately trained individuals, are even more dangerous.

This isn't the case here, in my opinion. Dr. Snider.

DR. SNIDER: Well, on the first issue, I think I would not like to leave the room with the

notion that we considered this and decided not to do it and that's the end of the story.

To me, the issue that's being raised is a very important issue and we should go on record as a committee I would hope, as being concerned about the issue -- and I think we are, from all the comments -- concerned about the issue of provider education, about the risk associated with oral polio vaccine, and provider education about the options available, and parent's or potential recipient's education about the potential options.

And that we should explore -- "we" being CDC, FDA, professional societies, advocacy organizations -- we all should consider this a serious problem and try to work together to figure out what are the appropriate solutions.

Secondly, with regard to boxed warnings, I personally would like to know if there is information -- and if there's not information would be interested in it being gathered -- on what impact boxes have. Because I can think of certain criteria as you've articulated, as reasons I would want to give a special alert, if you will.

But I still don't know whether -- I mean, certainly the box doesn't seem to be conducive to

talking about options. So what is the box going to do? What does it accomplish, and is it the best way of conveying information, and if so, what type of information?

And that's a scientific issue, too. It's in the area of risk communication, but it's an issue that can be addressed scientific. And I think it would behoove FDA to try to get more information about that particular approach to risk communication.

CHAIR FERRIERI: Dr. Zoon.

DR. ZOON: Yes. In addressing the impact of a boxed warning, we currently do not have that data, but we will go back and check with our colleagues for the Center for Drugs and see if they have any information related to that as to the impact.

And I also would like to say, we would look forward to working with the CDC and physician organizations to see if we could do a better job at educating physicians, nurses, and helping in any way we can getting the information to the parents.

So, thank you.

CHAIR FERRIERI: Thank you, Dr. Zoon. One last comment, Dr. Evans.

DR. EVANS: I'm just going to tag onto that a little bit. There's been a lot of movement in the

area of vaccine risk communication. We have a vaccine safety action plan that the Public health Service has been putting together with Rob Breiman kind of overseeing it, and a major component of that is vaccine risk communication, specifically assessing what providers know, what parents know, and ways that we can better educate, get tools to them, and get some empiric data on what kinds of things work and don't work.

And so in response to someone's comment about this thing about education being vague, there's an unprecedented amount of movement in this area and there's going to be much more, because unfortunately we live in a world in which vaccine safety issues seem to be everpresent.

CHAIR FERRIERI: Thank you very much. I want to really thank the people who came for the open public hearing. I know what it took emotionally to come and present to us, and you've really accomplished it more than you might have imagined at the end of this meeting.

You've stimulated quite a reaction that will continue much beyond the length of this meeting this afternoon. And I think the FDA and the government, the Public Health Service, takes this issue very, very

seriously, and I think we will all gain because of the efforts that you all have made.

So we may not have accomplished everything that you had hoped for, Dr. Baylor, but from my point of view I think it's opened up an incredibly big area for us to contribute to in the future.

So I would like to thank you and also indicate adjournment.

(Whereupon, the Open Public Hearing was adjourned at 5:40 p.m.)

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FOOD AND DRUG ADMINISTRATION CENTER FOR
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DATE: May 27, 1998

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