UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

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PEDIATRIC ADVISORY SUBCOMMITTEE

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MEETING

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TUESDAY,

JUNE 11, 2002

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The Subcommittee met in the Versailles Room of the Holiday Inn, 8120 Wisconsin venue, Bethesda, Maryland, at 8:00 a.m., Joan P. Chesney, M.D., Chairperson, presiding.

PRESENT:

JOAN P. CHESNEY, M.D., Chairperson

THOMAS H. PEREZ, R.Ph., M.P.H., Executive Sec.

DAVID DANFORD, M.D.

STEVEN EBERT, Pharm.D.

PRESENT (Continued):

ROBERT FINK, M.D.

MARY GLODE, M.D.

RICHARD GORMAN, M.D.

MARK HUDAK, M.D.

RALPH KAUFFMAN, M.D.

NAOMI LUBAN, M.D.

ROBERT NELSON, M.D., Ph.D.

JUDITH O'FALLON, Ph.D.

VICTOR SANTANA, M.D., Ph.D.

STEVEN SPIELBERG, M.D.

ALSO PRESENT:

DEBBIE BIRENBAUM, M.D.

LILLIAN BLACKMON, M.D.

JULIA DUNNE, M.D.

ROBERT EASTEP, M.D.

GEORGE PERRY, M.D.

HUGO GALLO-TORRES, M.D.

JERRY GARDENER, M.D.

BENJAMIN GOLD, M.D.

ERIC HASSALL, M.D.

MARTH HELLANDER, J.D.

ALSO PRESENT (Continued):

LAURA JAMES, M.D.

GREG KERNS, M.D.

DIANNE MURPHY, M.D.

VICTOR RACZKOWSKI, M.D.

ROSEMARY ROBERTS, M.D.

WILLIAM RODRIGUEZ, M.D.

AGNES ST. RAYMOND, M.D.

JOHN WALKUP, M.D.

ROBERT WARD, M.D.

BENJAMIN WILFOND, M.D.

ANNE WILLOUGHBY, M.D.

HARLAND WINTER, M.D.

C-O-N-T-E-N-T-S

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:12 a.m.)

CHAIRPERSON CHESNEY: Good morning, and my name is Joan Chesney, and I'd like to welcome everyone to this morning's session on the use of proton pump inhibitors for gastroesophageal reflux disease in children.

The uses of these agents without appropriate labeling has increased over the last few years, and particularly in infants under one year of age. The agency has developed a template for pharmaceutical agents to help direct their studies for these agents, and the questions for us this morning are basically threefold.

The first one has to do with whether efficacy studies should be considered for infants under one year of age because gastroesophageal reflux disease in infants manifests itself generally with respiratory in supraesophageal symptoms as opposed to those symptoms in older children.

And, secondly, their question for the committee is that if the committee agrees with the

concept of efficacy studies in infants under one year of age, are the randomized withdrawal design studies they've proposed acceptable, and what should the endpoints be?

And, thirdly, are the PK and PD studies recommended for children over one years of age appropriate?

So with those introductory comments, I did want to thank the group that put together all of the references for the committee, which I thought were very appropriate and focused, and for those of us not in the area, it would have taken weeks of work to identify these papers.

So let me start then by asking if we could go around the room and have everybody introduce themselves, and maybe I'll start with Dianne.

DR. MURPHY: I'm Dianne Murphy, and I'm the office director of the For Now, and we'll talk a bit more about this later, Office of Pediatric Drug Development and Program Initiatives.

DR. RACZKOWSKI: Good morning. I'm Victor Raczkowski. I'm the Acting Director of the

Division of Gastrointestinal and Coagulation Drug Products, the division that put together the proton pump inhibitor template.

DR. BIRENBAUM: Good morning. I'm Deborah Birenbaum. I'm medical team leader for the new Division of Pediatric Drug Development and one of the medical officers who consulted on this project.

DR. GALLO-TORRES: Good morning. Hug Gallo-Torres. I am a medical team leader in the Gastrointestinal Coagulation and Drug Product Division.

DR. O'FALLON: Judith O'Fallon, biostatistician at the Mayo Cancer Center.

DR. LUBAN: Naomi Luban. I'm Vice Chair of Laboratory Medicine and Pathology at Children's Hospital National Medical Center, George Washington University.

DR. GORMAN: Richard Gorman, pediatrician in private practice in Ellicott City, Maryland.

DR. FINK: Bob Fink, pediatric pulmonologist, Washington, D.C.

DR. DANFORD: David Danford, pediatric

cardiologist, Omaha, Nebraska.

DR. SANTANA: Victor Santana, pediatric oncologist, St. Jude's Children's Research Hospital in Memphis, Tennessee, and the University of Tennessee.

DR. NELSON: Robert Nelson, pediatric critical care medicine at Children's Hospital in Philadelphia.

CHAIRPERSON CHESNEY: Joan Chesney, pediatric infectious disease, the University of Tennessee Health Science Center in Memphis.

DR. PEREZ: Tom Perez, Executive Secretary to this meeting.

DR. EBERT: Steve Ebert, a clinical pharmacist in infectious diseases at Meritor Hospital and Professor of Pharmacy, University of Wisconsin, Madison.

MR. HUDAK: Mark Hudak, a neonatologist at University of Florida, Jacksonville.

DR. HASSALL: Good morning. Eric Hassall, pediatric gastroenterologist, Vancouver, British Columbia.

DR. FERRY: I'm George Ferry, a pediatric

gastroenterologist at Baylor College of Medicine in Houston, Texas.

DR. GOLD: I am Ben Gold, a pediatric gastroenterology, Emory University in Atlanta, and the Director of the Helicobacter Lab at Centers for Disease Control in Atlanta.

DR. KAUFFMAN: I'm Ralph Kauffman. I'm Director of Medical Research at Children's Hospital in Kansas City, Missouri, at the University of Missouri. I am here partly representing the Academy of Pediatrics.

DR. WILFOND: I'm Ben Wilfond, a pediatric pulmonologist with the National Human Genome Research Institute and also with the Department of Clinical Bioethics at the NIH.

DR. WARD: I'm Bob Ward, a neonatologist, University of Utah.

DR. BLACKMON: Lillian Blackmon. I'm a neonatologist recently retired from University of Maryland, and I'm partially here APP Chair, Committee on Fetus and Newborn.

DR. WINTER: Harland Winter, a pediatric

gastroenterologist, Mass. General Hospital for Children in Boston.

DR. JAMES: Laura James. I'm a pediatric pharmacologist at Arkansas Children's Hospital in Little Rock, Arkansas.

DR. SPIELBERG: And Steven Spielberg, Pediatric Drug Development at Johnson & Johnson, representing PHRMA.

CHAIRPERSON CHESNEY: Thank you, and we'll let Tom Perez give the meeting statement next.

DR. PEREZ: Thank you.

Good morning. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The Food and Drug Administration has prepared general matters waivers for the following special government employees which permits them to participate in today's discussion: Dr. George Ferry, Dr. Robert Fink, Dr. Richard Gorman, Dr. Eric Hassall, Dr. Naomi Luban, and Dr. Victor Santana.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30 of the Parklawn Building.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they may apply to the general topics at hand. Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each number.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

With respect to FDA's invited guests, there are reported interests that we believe should be made public to allow the participants to objectively

evaluate their comments.

Dr. Lillian Blackmon is participating as an expert in neonatology and is not representing the opinions of the National American Academy of Pediatrics Committee on Fetus and Newborn.

Dr. Benjamin Gold received speaker fees from TAP Pharmaceutical, AstraZeneca, and ASAI. He is also a scientific advisor to TAP Pharmaceutical, Wyeth AstraZeneca, and ASAI.

Dr. Laura James is a co-investigator on a Wyeth-Ayers sponsored study of the pharmacokinetics, pharmacodynamics, safety and tolerability of intravenous pantoprazole in hospitalized pediatric patients. She is consulting with AstraZeneca concerning the development of a pediatric esometrazole program.

I forgot my glasses.

Dr. Agnes St. Raymond is a full-time employee of the European regulatory authority, European Medicines Evaluation Agency. She deals with pre-licensing activities of medicinal products.

Dr. Steven Spielberg is Vice President,

Pediatric Drug Development at Johnson & Johnson.

Dr. Robert Ward is a co-investigator for Abbotts Ross Products Division. He also receives consulting fees from Wyeth-Ayerst, McNeil Consumer Healthcare, Janssen Research Foundation, and ZARS, Incorporated.

Dr. Harland Winter is an officer of the Children's Health and Nutrition Foundation; is negotiating support for an educational program with TAP, Wyeth, AstraZeneca, Janssen, Proctor & Gamble, and Olympus. Dr. Winter previously completed research trials for AstraZeneca, Janssen, Proctor & Gamble, TAP, Reliant Pharmaceuticals, Celltech and Centicore. He is currently an investigator on trials for TAP, Centicore, and Proctor & Gamble.

Dr. Winter also consults for AstraZeneca, TAP, and Janssen. Additionally, he is a member of the Speakers Bureau for Proctor & Gamble, and receives speaker fees from Centicore.

Further, he is a scientific advisor to AstraZeneca, TAP, and Janssen.

Dr. Ralph Kauffman is currently involved

in research studies for Janssen, Bristol-Myers, Squibb, and Merck. He is also a scientific advisory for McNeil Consumer Products, Johnson & Johnson, and Purdue Pharma.

Dr. Walkup has contracts grants from Eli Lilly, Wyeth-Ayers, Solvay, and Pfizer. He also receives speaker fees from GlaxoSmithKline, Solvay, and Janssen.

In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

That concludes the meeting statement.

I'd also like to make a couple of announcements. One, these microphones are on all the time. So they will pick up whatever discussions you're having. So everything will be on the record.

Okay. In addition, the agenda that has been passed out, there are two words that made it onto the agenda that should have been stricken. At the very top, GERD template. I apologize to anyone who thought we were not coming back from lunch. We must kill any rumors that FDA only works half days. So this is going to be a long day.

Thank you.

CHAIRPERSON CHESNEY: Thank you, Tom.

And now Dr. Murphy is going to make opening comments.

DR. MURPHY: Yes. Thank you.

First of all, I would like to welcome back -- it's delightful to see the Pediatric Advisory Subcommittee as you enter into your fifth year of providing advice and guidance to the agency. That's a pretty exciting statement, I think, that we are now in the situation in which we have enough issues to discuss pediatric drug development on at least an annual basis. And as you well know, we anticipate that you will be meeting more frequently in the future.

With the passage of the Better Pharmaceuticals for Children Act, which we will speak more about tomorrow as the subcommittee will be participating in a training session on that. So we will be focusing today on the result of what we are glad to say is an evolutionary process that we're seeing as we are able to ask for studies to be conducted in children, learn from the science that is evolving, and come back and seek additional input and advice.

We have always said that we anticipate this whole process will be one in which we learn, and we will need to reevaluate what we've learned, and to then restructure how we proceed in asking for additional studies.

And the package that the division has put together this morning for you reflects that progress and evolution, and it's actually quite exciting to be able to do this at this point.

I think the other point about the discussion this morning is that we usually have at least a half day of ethical issues for this committee.

We have not neglected that. I'm sure you're aware if you read your package that there are ethical issues to be discussed in the trial designs that are being brought to you today.

So you have a very full day. When I saw the questions the division had developed I thought we really needed to extend the agenda to about eight o'clock tonight, but I know Joan will keep you guys on track and keep you moving because you have a tremendous amount of work.

So I'm not going to say too much more, except to say that the rest of today we are then going to bring to you one of the new tasks that you have been asked to participate in, which is the development of work with the National Institutes of Health and the FDA in developing a process for a priority list of products to be studied, and these products need to be off patent.

For the rest of the day when we say off patent, we're going to be referring to both off patent and those products without any remaining exclusivity, just to shorten the verbiage.

And we are also very pleased today to have our guests from Europe. We've worked extensively -- the agency has -- with many of the regulators in Europe to be able to move forward on a global manner of the development of products for children, and they are going to update you on the progress that is being made in Europe. And I think that will be very interesting for the committee to hear.

It's a very different process. If we think our lives are complicated, wait until you hear about theirs.

And I will end right there except to again say that we wish to thank everybody for being here, committing their time, their effort. I think that the agency benefits tremendously from the discussions, and I know the science of our trial development benefits from these discussions, as does the thoughtfulness of the ethical discussions.

And we look forward to the rest of the day.

Thank you.

CHAIRPERSON CHESNEY: Thank you, Dr.

Murphy.

We have a lot to do this morning, and I'd like to ask if you could hold questions for the speakers until just before the break. If we don't have anybody speaking in the open public hearing, we'll have a half hour there, and if we do have somebody, we still may have some extra time there.

So if we could start with Dr. Hugo Gallo-Torres talking about an introduction to the proton pump inhibitors, the written request template.

DR. GALLO-TORRES: Good morning. Thank you for the opportunity. This is a very exciting occasion, indeed, particularly for the opportunity of introducing the theme of conversation/interaction today.

My name is Dr. Hugo Gallo-Torres. I am a medical team leader of the Gastrointestinal Coagulation Division.

This is an outline of the topics I'm going to be briefly mentioning. These titles and some titles will show up in the next slides.

It is important as an introductory

statement to say that the pediatric written request is a voluntary program -- sponsors do not have to do it -- that provides financial incentives to companies for conducting needed studies of drugs that may produce a health benefit to the pediatric population.

The PPI template for written requests is used in the treatment of gastroesophageal reflux disease, GERD. As part of the rationale, I would like to simply say a couple of things.

Information relating to the use of PPIs may produce a meaningful health benefit in the treatment of GERD, as we said, in the pediatric population. Please note that we have chosen GERD because this is more prevalent than other indications, such as duodenal ulcer, gastric ulcer, and so on.

We also know that proton pump inhibitors are widely used in pediatric patients, and we know this from published treatment algorithms for pediatric patients with GERD, and we also know this from the usage data available, such as the IMS health data provided to you in the briefing document.

Two points regarding the extrapolation of

efficacy data. FDA regulations permit extrapolation of adult efficacy data to pediatric patients when? When there is similar course of the disease in adults and pediatric patients and when there is similar drug effects in adults and pediatric patients.

Of course, all of the information supporting pediatric use also is needed.

What I'm going to do next is to contrast the two main age groups, that is, those who are less than one years of age and those who are one year of age or older.

The course of GERD in adults, we believe, is not sufficiently similar to the course of pathological gastroesophageal reflux in this group to permit extrapolation for the adult efficacy data. Therefore, the PPI template does require, does request efficacy studies in this pediatric patient group.

In the one year old group, the course of GERD is sufficiently similar to the course of GERD in adults to permit extrapolation of efficacy. Therefore, the PPI template does not request efficacy studies in this pediatric age group.

This is a table of the requested studies by age group, and you can see that the studies go all the way from neonates and pre-term infants to pediatric patients 16 years of age.

You also notice that thick line here separates the studies in patients who are less than 20 months of age versus those who are older.

Listed here are the components of the different studies: pharmacokinetics, single and repeat dose; pharmacodynamics; exposures and response; efficacy, and safety.

You notice that pharmacokinetic studies are requested throughout for all the studies, and so are safety studies. So these are dissimilarities that will not be stressed any longer.

What I'd really like to do is to mention the dissimilarities, especially the pharmacodynamic and the efficacy components. As you can see from this table, the PPI template requests the pharmacodynamic studies in this group and in this group, but not in children who are one year old or elder.

And the main reason to do is because we

believe that data from adults can be extrapolated to this group of patients.

Similarly, the template requests former efficacy studies. These studies are to be powered for efficacy in these two groups of patients, but not in these for the same reason.

What I would like to do next is to briefly discuss selective individual studies by age group, and here the handout provided to you has a lot of these statements. So I will not repeat some of them. They will just show up in the slide.

In the 12 years to 16 years of age, Study 6, there is a pharmacokinetic and safety component. The patient population is patients who have a clinical diagnosis of suspected GERD. The PK component is a randomized pharmacokinetic safety study of at least two levels of the proton pump inhibitor for single and repeated dose. Either traditional or population PK analysis can be used, and repeated dose of PPI levels are selected on the basis of results from the PK component.

Study 6 has an eight week safety component

of at least 100 patients. This is a multi-center, open label, nonrandomized, eight weeks in duration study.

Next one, please.

In the one year to 11 years of age group, the PPI template requests Study 5, and this is a pharmacokinetic exposure response and safety study. The patient population consists of patients with endoscopically proven GERD. The exposure response and safety component where we request at least 80 patients, 40 of these in the one to five year and 40 in the six to 11 years of age, a more or less representation of the different age groups. It is randomized, double blind, dose ranging with eight-week treatment.

It is very important to stress that this study is exposure response study. It's not powered for efficacy.

In the one month to 11 month of age of Study 3, we have a pharmacokinetic, pharmacodynamic and safety study. The study population, and this is Study 3, are hospitalized patients, candidates for

acid suppressive therapy because of a presumptive diagnosis of GERD.

There's a pharmacodynamic and safety component to this study randomized at least to those levels of the PPI. Changes in intragastric and/or intraesophageal pH are requested. Pharmacodynamic assessments in patients that require tube placement or pH monitoring for clinical management is requested.

It's important to point out that the tube placement is not done for the purpose of the study. It's not necessarily related to the protocol.

In Study 4, efficacy and safety study, the patient characteristics are those of clinical diagnosis of suspected GERD. It is important to point out here that acute, life threatening events due to GERD are excluded in Study 4.

And it is also important to point out that resource tests used to establish the diagnosis will be provided, even though the test may not support the so-called diagnosis of suspected GERD.

In the one months to 11 months of age, we also have a Study 4, and all I'm going to say here is

that there are several publication provided to you, especially from Dr. Temple, addressing the advantages and disadvantages of using the treatment of withdrawal design.

What I should like to do is to stress certain issues related to the design. The endpoints in Study 4 are supraesophageal and airway complications associated with GERD; GERD signs and symptoms; growth parameters; frequency, severity, and duration of wheezing; and assessment of compliance.

Study 4 is powered for efficacy, and we have now arrived to what we believe is probably the most interesting type of studies, those studies in neonates and pre-term infants with a corrected age less than 44 weeks.

And here we have two studies, one and two. Study 1 is a pharmacokinetic/pharmacodynamic and safety evaluation. Who are the patients in this study? The patients in this study are monitored patients admitted to a newborn intensive care unit or a special are nursery who have evidence of obstructive apnea, who are candidates for acid suppressive therapy

to treat a presumptive diagnosis of GERD, and whose body weight is at least 800 grams.

This pharmacodynamic component is not too dissimilar from the one we saw in the one to 11 months age group. Excuse me, please.

There's a safety component to Study 1. Apnea and bradycardia are assessed concurrent to pH metric.

Study 2 is an efficacy and safety study. The patient characteristics are the same as for Study 1. Again, you have already seen or heard the design of Study 4 for pediatric patients one to 11 months of age.

In Study 2 the outcome measures are different, and rather than going through this information that we already mentioned, I would like to stress certain aspects of the design of Study 2, and here they are.

Study 2 is stratified for methylxanthine and corrected by age. In this study it's important to consider whether the patient is receiving concomitant prokinetic agents, such as metoclopramide or

erythromycin, theophylline agonist (phonetic). The patient, of course, may very well need these medications, but these medications may be confounders. So we need to take this also into consideration.

This is a very important point to stress. Patient enrollment and efficacy is measured by obstructive apnea, and obstructive apnea is assessed by pneumograms.

I should also like to mention that additional outcome measures in the Study 2, and these include patient discontinuations due to ineffective treatment, apnea as assessed by conventional cardiorespiratory monitoring, and nursing observations, and severity of apneic episodes.

Study 2 is powered for efficacy.

Then I'd like to mention additional safety measures, such as listed in there: overall mortality, adverse events, including co-morbidities of prematurity and growth.

The withdrawal phase of Study 2 is important because the protocol will define discontinuation criteria due to adverse events or

insufficient therapeutic effect, in other words, treatment failure.

And therapy for central apnea should be dropped. There's a long-term safety component to Study 2.

So we have now arrived to the overall summary, and it is important for us to rate the following.

Number one, adult efficacy data cannot be extrapolated to pediatric patients less than one year of age.

Number two, efficacy of proton pump inhibitors in the treatment of gastroesophageal reflux disease in pediatric patients less than one year of age must be established in adequate and well controlled clinical studies briefly summarized for you here.

Number three, we believe that the randomized withdrawal design can minimize prolonged exposure to placebo in situations where inclusion of a placebo arm may be felt to be undesirable or not feasible.

Number four, the written request has provisions for prompt discontinuation from randomized study therapy when discontinuation is felt to be clinically appropriate.

Number five, for pediatric patients more than one year of age, the efficacy of the proton pump inhibitor in the treatment of GERD may be extrapolated from efficacy studies in adults.

And, finally, for all pediatric populations, adequate pharmacokinetic and safety information is needed.

Thank you very much for your attention.

CHAIRPERSON CHESNEY: Thank you, Dr. Gallo-Torres.

And our next speaker is Dr. Eric Hassall, who will be speaking about pathologic pediatric gastroesophageal reflux and clinical trial design, differences between infants under one and over one year of age.

DR. HASSALL: Good morning, everybody. Thank you very much for the opportunity to speak on this topic today.

This is what I'm going to talk about. The outline, a little bit of background; the difficulties in doing pediatric clinical studies; a couple of definitions; brief mention of complications and goals of treatment; mention of prevalence and natural history in different age groups; available treatments; a little bit about pathophysiology mechanisms; etiologies; acid secretions; underlying diseases; a brief mention of pharmacokinetics; focus really for a little bit on endpoints; feasibility; and for my own view of what the requirements are for performance of a successful study.

The difficulties in doing pediatric studies are as follows. I'm not going to address the ethical issues because one of the other speakers is going to do that.

Of course, we know that there are age related differences in disease manifestations.

The fears of parents, the fears of investigators.

Feasibility; what's practicable in various age groups.

The time and labor intensiveness of dealing with children and their families is something definitely to be reckoned with.

The need for flexibility. There may be some studies in which certain tests might need to be options. Certainly in one of our other studies we built one of those, that flexibility in.

And the inexperience of pediatric centers. As you know, the recent push for doing studies in children will lead to some enormous benefits, but at the present time, there are many centers who are just gearing up really with expertise in order to do some of these studies.

A brief mention about definitions. GERD is a term that's tossed around fairly loosely. I just want to differentiate between gastroesophageal reflux and gastroesophageal reflux disease, GERD, in other words, the presence of a complication. These complications include esophagitis; peptic stricture; Barrett's, which does occur in children, albeit with fairly low frequency; failure to thrive; pulmonary or ENT, ear, nose and throat disease, supraesophageal;

Sandifer's Syndrome, or torticollis.

What are the management goals? I think we can agree, hopefully, that the common goals that we're testing are to relieve symptoms, to prevent complications, to heal esophagitis, to maintain remission, and to treat complications.

It's going to give my neck a break from this side.

Okay. A brief mention about prevalence and natural history. Suzanne Nelson has done a couple of terrific studies. This one, 1997, prevalence of symptoms of reflux during infancy, cross-sectional community, practice based, almost 1,000 healthy children below 13 months of age.

The infant GER questionnaire devised by Sue Orenstein has been shortened and revised. That only takes five minutes rather than the approximate 20 minutes that the original took. The main outcome measure is the reported frequency of vomiting.

In terms of her results, vomiting was found to occur at least once a day in half the children below three months; at least once a day in

five percent at ten to 12 months; a peak frequency occurred at about four months of age; and there was a decrease from 61 percent to 21 percent between six to seven months of age.

You can see this very dramatic drop-off between these months. The peak frequency of vomiting was reported to be a problem by parents, 23 percent at six months and dropping off again further to 14 percent at seven months.

Now, I'm not going to quote all of Suzanne Nelson's studies or the others, but I'm just going to summarize them to say that the natural history of the disease is below two years of age, very often, almost always physiological, especially below the age of six months, 90 percent resolved within 12 to 18 months. These are -- I'm sorry I left the dates of here -- data from Carr and Nelson.

Above the age of two years to adulthood, first of all vomiting above the age of two years is never physiologic. GERD is usually a chronic relapsing disease in the over two year old child, as it is in adults.

The presentation, the age related presentations at around two to four years of age, similar symptoms and signs to younger children. Heartburn is very unusual, again, from one of Dr. Nelson's studies.

Above the age of eight to ten years, the signs and symptoms are similar. Presentation depends on the nature. The nature of vomiting may be effortless versus forceful or projectile. The disposition of the child, in other words, what we do with these children, and how we investigate them or not differs between the fat, happy spitters, those children who are thriving versus the unhappy, irritable child who may have poor weight gain, in other words, the child with a complication.

What about available treatments? Well, the different managements that are employed include explanation, reassurance, diet, life style, position, antacids, anticholinergics, botanicals gone out of vogue, prokinetics. Metoclopranide is not a good drug in children. Cisapride is not available to us. I forgot to mention erythromycin. H2 receptor

antagonists, and then the old standbys of prayer, meditation, Vega therapy, and the cause of all ills, Candida treatment or Candida as a problem, rather.

But really what I'm going to focus on is the treatment of severe GE reflux disease, big league GE reflux disease, and for that we've got anti-reflux surgery, PPIs. I've put endoscopic treatment in parentheses because it's in its infancy, and hopefully it will not make it to children for several years.

Why is anti-reflux surgery important? Excluding minor procedures, like Inguinal herniorrhaphy, central line placement, in the United States anti-reflux surgery is the commonest operation performed by pediatric surgeons.

I should just mention that in the years 1993 until the year 2000 at our institution in Vancouver, British Columbia, with the judicious selection of patients and use of PPIs, we have cut our annual operation rate from 50 anti-reflux procedures per year to approximately five new anti-reflux procedures per year.

A brief word about etiologies underlying

diseases and mechanisms, and I'm really just going on focus on underlying disorders.

We know that the conditions predisposing to the worst GE reflux disease are as follows: neurologic impairment -- I won't go through all of the reasons for these, but I can certainly address these if there are questions -- neurologic impairment, a variety of reasons; repaired esophageal atresia. This is an esophagus that's never functioned properly in utero, even if surgical continuity is established. Chronic lung disease.

And then in children who don't have underlying systemic diseases, I believe that hiatal hernia is a very under recognized cause of GE reflux disease, certainly if one knows how to recognize it endoscopically, it is present in my experience in almost every patient with Barrett's esophagus and almost all patients with erosive esophagitis.

And then, of course, the mechanism of transient lower esophageal sphincter relaxation.

What about acid secretion? We're talking about using acid suppressing drugs, but what about

acid secretion? Does it occur in children?

A couple of excellent studies that have been done. In healthy term infants, there is relative hypochlorhydria only for the first zero to five years of age, normalizing by about six to eight hours of age. The normal basal acid output of 25 plus or minus ten micromoles per kilo per hour approximates that in adults.

Hypergastronemia occurs despite normal acid secretion. A study by Art Euler, who I believe is in the audience, 1977.

Paul Hyman, in Gastroenterology in 1983, a colleague also at UCLA with me. Enteral feedings are necessary for normal oxyntic mucosal secretion. In the purely TPN fed child, these children are relatively hypochlorhydric.

Paul Hyman also showed in 1984 that meal stimulated secretion occurs, but it's weaker than in older infants, in other words, those above six months.

Again, Dr. Hyman showed this time in healthy pre-term infants that basal acid output by seven days of age was relatively low at 12 micromoles

per kilo-power (phonetic), increasing over the first month of life to within the older child and adult ranges of about 30, again, micromoles per kilo-power.

And very few infants are, in fact, achlohydric, and it's pentagastrin-fast achlorhydria in the first week of life.

So, in summary, with regard to acid secretion, yes, pre-term and term infants do make acid. So these drugs are definitely relevant to us. Acid secretion increases rapidly to that within adult ranges on the basis of micro moles per kilo-power.

Pentagastrin responsiveness occurs by one to four weeks of age. The increase in secretion depends not on gestational age. Rather, it depends on postnatal age.

And infants require enteral feeds for normal acid output.

A brief word on pharmokinetics. I know we've got individuals in the audience and speakers who are much more expert than I at this. I'm just going to quote one of the studies I was involved in.

For omeprazole, and this was published by

Tommy Anderson in our group who did the pediatric international omeprazole study, a study between six centers in Canada, some centers in Europe, Britain, and Australia, and our own international clinical study.

We know that the ontogeny of metabolism, the metabolic capacity, meaning these parameters, area under the curve, area under the curve normalized, the t-half, the Cmax, and the Cmax normalized, are highest between the ages of one and six years. We did not study any children under the age of one year in these studies; and that there is a gradual decline in metabolic capacity with increasing age to reach normal adult values by approximately 12 years.

And this accounts for the findings that much, much higher doses on a per kilo basis are required in the younger children than in older children and adults.

So if, for example, we extrapolate the dose ranges that we found in our studies, for example, approximately .7 to three milligrams per kilo per day in a 70 kilo adult, you can see what kinds of doses

those would translate to.

And so the question is also if the PK characteristics are similar to the benzodiazapines, can we extrapolate to the under one year of age children.

And I think now to really the meat of my topic today, and that is looking at the endpoints, systems and signs and feasibility.

For the purposes of a study, in my view, the symptoms and signs should be definitely causally related to gastroesophageal reflux disease, most relevant to patient improvement, something we want to improve for the patient's benefit, prevalent, highly prevalent in the age group under study, measurable, hard, objective, safely accessible in the given age group, physically accessible in the given age group.

And by feasibility, I mean the ability to accrue an adequate number of patients in each age group to retain these patients in the study, and of course, these are integral to the success of the study.

So, again, this is my own little table

drawn up just to see, and there may be other factors here, just my own view. This is not published at all.

I would propose the presenting symptoms and signs, the endpoints be subjected to at least some of these tests: vomiting, for example, frequency; heartburn and esophagitis.

Well, we know that vomiting is highly prevalent. We can measure its frequency. It's prevalent in all age groups.

Heartburn we know is only describable in certain age groups and certainly not in neurologically handicapped children. Esophagitis is definitely a hard endpoint in all age groups.

Then the question is: what about the degree of acid reflux, intraesophageal pH? Is that useful?

I've put a check mark and a question mark because although we can show that intraesophageal pH -- the degree of 24 hour acid exposure is decreased by agents. Does that relate directly to symptoms? In our own studies, we actually showed that it did in several mepiprazole studies.

And, in addition, there are some linsoprazole studies that I'm aware of using the same methodology.

Epigastric pain and irritability. Now we're getting onto slightly softer endpoints, much more subjective. Again, these may be the only parameters we have to use in such age groups, but we must acknowledge that these are softer.

What about failure to thrift? Actually weight gain is a good parameter in young children. It's not such a good parameter in older children necessarily, but of course, there are many other factors that go into it.

Then feeding problems, a very soft endpoint, very sort of catch-all phrase.

Respiratory problems, supraesophageal problems, dysphagia or odynophagia are very seldom complained about by children. Apnea, my own view is that apnea is not a good endpoint for children because it's -- and I'm sure we'll get more into this in discussion.

My own reading of the literature is that

there's a very poor correlation between apnea and gastroesophageal reflux disease; also to mention that it's exceedingly difficult to study this particular parameter in infants.

And then, of course, are we interested in the degree of acid suppression, in other words, the intragastric pH changes? In my view we're not that interested, other than doing PD studies, but we're not that interested for the benefit of the particular patient. We're not aiming to make the achlorhydric. We're just aiming to decrease the amount of acid reflux into the esophagus.

So, in summary, my own proposed requirements for performance of a successful study in children are it depends on the availability of other equal or better treatments. This may impact our ability to offer placebo.

Is the question that we're asking worthwhile? Is the protocol simple? Are the tests reliable? Are the tests not overly invasive, given the child we're studying?

What about the parents? Of course, we

need willing parents to enroll these children, and we need the docs to be willing to discuss enrollment with parents.

And finally, as I alluded to before, we need pediatric studies that are qualified to carry out the specific proposals.

So a couple of questions. Dr. Gallo-Torres has already addressed a couple of these, and I'll just ask them as questions.

Is the age group less than the dividing line, less than one year versus one to two years and up to 17 years; is this a sufficiently sensitive or adequate age group breakdown? Do we need others? And what should they be?

Are there indications for PPI use in all age groups? I think that's a basic question we do need to ask. Do we need PPIs under the age of a year?

Efficacy. Can we study it in all age groups? If not, can we impute efficacy from other studies? It may be very, very difficult to study efficacy in some age groups.

What are the appropriate study endpoints

in each age group? And what are the dosages?

And of course safety in each age group.

Thank you very much.

CHAIRPERSON CHESNEY: Thank you, Dr. Hassall.

Our next speaker is Dr. Hudak, a member of the committee who's going to talk about clinical trial design related to studies of protein pump inhibitors in the neonate and the premature infant.

DR. HUDAK: Good morning. I've been tasked with a formidable number of assignments here to get done in 15 minutes, but I just want to review what those issues are.

And the primary task was to talk a little bit about the huge controversy that exists in our field with respect to any association between apnea and gastroesophageal reflux. Like many other things in our field, despite 20 years of intense study and debate and literature, this is still not clear.

I was also tasked with talking about what the current management of apnea associated, GR associated apnea is. Is there a standard across the

country?

And the answer to that I think you'll see is no.

To talk a little bit about issues with respect to clinical trials in this very different population of premature infants and neonates less than one month of age.

And then finally, some specific issues with respect to potential trials of PPIs in this population, touching upon some of the clinically meaningful outcome measures and some of the other measures, short and long-term efficacy safety measures.

So just to review here, gastroesophageal reflux is, I think, when we talk about it, it means one of two things. One is regurgitation, and the other is sort of just reflux that's caused by relaxation of the lower esophageal sphincter, and depending upon whether you're a lumper or a splitter, you're talk about these things separately. I mean, they clearly have different sorts of mechanisms. They have different prognoses.

Having lost about four or five ties when my son was about three to five months old, I'm well aware of the regurgitation phenomenon. That's a very self-limited one.

The actual reflux itself that may not manifest with regurgitation is typically caused by relaxations of the lower esophageal sphincter.

Both of these things, regurgitation and reflux are considered to be really physiologic because they're both very, very common in premature babies and term infants. And if you look at the information that's been done in healthy term infants -- and there are articles in the handout that go through that -- the sort of incidence of reflux studied by pH probe or other means sort of peaks at about three to five months of age in terms of the number of episodes per day; in terms of the reflux index, which is the percent of time that the esophagus sees a pH less than four; and in terms of the maximal duration of an episode.

And then that sort of gradually abates, but never really clears. In fact, adults have -- for

pH probe in normal adults, you'd have reflux there, which would be asymptomatic as well.

Now, in terms of risk factors for reflux, there are a number. Positioning and posture is very important. Pretty much everything we do in the nursery is to encourage reflux in the premature population, and there are good reasons for that.

We tend to attempt to restrain babies in a careful way. There's no JCHO representatives at this meeting. We don't use restraints. We use the word "snuggle" or "nest" infants in a developmentally appropriate configuration.

(Laughter.)

DR. HUDAK: And they're very happy with that, but that puts them in a prone position and sometimes with the left side down, and these are things that tend to work against gravity and tend to drain stomach contents up toward the LES. So those are issues.

Positioning, of course, is something that has been linked with SIDS, and this is exactly the sort of positions that increase the risk of SIDS, but

we all have these babies on monitors. So we catch any potential problem quickly.

There are a number of things that will increase gastric pressure in babies, including how rapidly you feed babies or how rapidly babies sort of feed themselves; the intervals of the feedings; the type of formula that may be used, whether it's a breast milk or a higher osmolar type formula will make a difference.

There are abnormalities of the abdominal wall. For instance, the status post repair of gastroschisis, you sort of close the wall and there are forces that tend to increase gastric pressure.

Decreased lower esophageal sphincter tone, again, that is physiologic in premature babies. That tone increases over time, but at least in the early part it tends to be quite low. There are drugs that we use, such as xanthines, in babies that will decrease LES tone.

Abnormal esophagus you've heard about in terms of babies who have had repair of esophageal atresia, babies with hiatal hernia, other esophageal

abnormalities.

Lots of reasons that basis who are premature will have neurological abnormalities, whether it's immaturity, dismaturity, or frank neurological abnormalities or injury.

Term babies, status post ECMO, have been described by at least one author as having an increased tendency for reflux.

And finally, there are a number of factors that can cause babies to have delayed gastric emptying, and this, of course, will tend to increase the tendency to have reflux.

In terms of the diagnosis of reflux, most of the time in the nursery what we do is rely upon our clinical observation. So if the baby sort of is in bed and sort of has an asymptomatic spit and necessitates a bed change, that causes a lot of attention.

Occasionally with babies who have feeding related bradycardia and so forth, we will study them most of the time with a barium swallow or upper GI series. We rarely do pH probes these days. They have

sort of gone out of favor, at least in our area, although other institutions do use them.

There are manometric techniques that will look at pressure changes in the esophagus, and the newest technique that's been written about is this multiple interluminal impedance technique, which is much more sensitive than a pH probe because it will also detect nonacidic reflux into the esophagus. So you can actually see bolus of material, different levels of the esophagus, with this technique.

Now, the mechanisms, reported mechanisms that cause apnea in babies who may reflux, it's clear with healthy spitters, they have a mechanism that's very different than infants who may have apnea mediated by a laryngeal chemoreflex. And I tend to believe that both of these things happen. I think it has been well described in healthy spitters that the contraction of the diaphragmatic muscles and the abdominal respiratory muscles occurs at the same time that there is a reflex closure, anatomical closure of the larynx. So that's before any gastric contents make their way to the larynx that that happens, and

that is followed by some pharyngeal swallowing and maybe by a short period of apnea in term babies, very brief, not invariable by any means, and then by coughing and sneezing to a variable degree.

Babies who actually have reflux and get formula or gastric contents in their larynx, it does stimulate a laryngeal chemoreflux leading to airway closure; apnea, which may be prolonged, lasting over ten to 20 seconds sometimes; pharyngeal swallowing; and attempts to clear the airway in that respect.

so I think that really does happen, and that's been pretty well documented.

The question of whether or not esophageal reflux, that is, material makes it way somewhere in the esophagus, but not in the pharynx and not into the larynx, whether that is associated with apnea, whether it's an acidic reflux or nonacidic reflux, in my mind, looking at the literature, that can't be said with certainty one way or the other.

Now, this is a very voluminous literature. You only have a very small amount of literature in the packet. There are hundreds of articles literally

over the years looking at different populations with different techniques, making different statistical analyses, using different measurements.

And basically I sort of like to summarize my understanding, and this is all debatable, but my understanding of this literature is that apnea and reflux both occur commonly in pre-term babies. They co-associate. It is very much -- that doesn't mean they are causally related one to the other. It's very much like the old studies of necrotizing enterocolitis in babies where things like umbilical artery catheters were associated, but, in fact, NEC occurs in tiny babies who are very sick, who have UACs or have had UACs back then, and on careful examination of all that information, the UACs were not found to be a risk factor for NEC.

Similar to the association of IVH and RDS in pre-term babies, a very immature, very vulnerable population, co-morbidities, co-associate.

Now, the older studies that first described the association of apnea with reflux really failed to look at it carefully in terms of the

temporal relationship. That is, they found a lot of reflux in babies who have lots of apnea, but they couldn't relate one event to the other.

The more recent studies -- and I think there are three or four in the packet -- looking at the universe of premature infants, that is, infants with apnea and so forth, have really been unable to establish in the broad population any statistically significant correlation temporally between acid reflux, non-acid reflux, and apnea. And it's looking at it with pH probes, with multiple impedance techniques, or looking at just clinical regurgitation in babies, nursing observations, and so forth.

However, I think it's pretty clear that at least in selected subjects, that there is a population of babies who got fairly significant symptoms, who have apnea by definition since they're being treated with xanthines, that is resistant to xanthines, who do respond to positioning, thickening of feedings, and surgical anti-reflux procedures with a tremendous diminution of apnea.

And how that sort of happens is not really

clear as a mechanistic point of view, but that's an important population to identify because I think those are the patients who may demonstrate some benefit to medical anti-reflux therapy.

Now, what is the current practice for treating reflux? Well, positional therapy, postural therapy is universal. Everybody does that.

A variety of feeding manipulations. Again, I think the key here is babies who spit up have residuals, have apnea. They go on to continuous feedings where the feedings are put on a pump and given over one to three hours. So it decreases the amount of volume introduced into the stomach per unit time, decreases gastric distension and pressure, and the feeling is that that does in some babies tend to minimize apnea and reflux.

Decreased osmolarity, that commonly happens. Thickening of formula is very variable, very variable across the country. Some people think with thickening with rice cereal actually, even though you get some symptomatic relief, may make the esophageal reflux worse.

Medical therapy. Neonatologists are trigger happy with drugs. One of my major tasks when I come on service is to try to decrease the drugs from at least 15 down to, you know, ten or some manageable amount in the pre-term baby, but commonly babies are put on a variety of acid blockers. Ranitidine is the one that we use now.

Cisapride, before it was taken off the formulary basically for complications and for lack of efficacy, was very common. There's data in the packet that says that, you know, 70, 80 percent of babies were discharged on cisapride. We used to call it Vitamin C. Anybody who had a residual would go on cisapride. It's unbelievable.

And right now reglin (phonetic) had sort of gone out of favor when cisapride came in, and now there's a trend back, I think, across the country, taking an informal survey, to more use of metoclopramide for treatment of residuals, apnea, possible reflux.

Now, specific considerations in pre-term infants. This is an extremely vulnerable population

of babies. We have to really focus a lot on the risk-benefit considerations for any particular study. Treatment of one group of symptoms may cause side effects and adverse issues in another organ system.

We at least want to see that there's some rational physiologic basis to treatment so that is, you know -- with the PPI, if the rationale is it decreases acid production, the hypothesis would be that that by itself would decrease some of the perhaps vego-vagal reflex mechanism of apnea, and so forth, that we haven't proved exists, or it may change the distal esophagus so that it's much more protective against reflux. Those are very speculative sorts of things.

A lot of the reflux in babies is nonacidic because they get fed often and it's buffered. So making up a rational physiologic basis for PPI therapy in pre-term babies is a little bit iffy.

And then long-term follow-up is obviously very important. And one of the questions is what appropriate age for long-term follow-up, and in my bias it's somewhere between one to two years.

There are multiple co-morbidities and confounders in babies that we have to recognize. It's difficult doing studies in pre- to term babies because we can't ask them if they're having more heartburn. They sort of don't tend to respond to those sorts of questions.

It's important to conduct the studies have equipoise, and that's something that's often missing. There's some therapeutic skepticism about the intervention that you're using.

Knowing the natural history of the disease is important in terms of timing the therapy. So if you've got a condition that developmentally fades out, you can deceive yourself into thinking the treatment is effective if you don't have controls.

Meaningful clinical endpoints are sometimes very difficult to come up with. I think in this case we'll talk a little bit about what those are in this population.

And then finally, the selection of the population is critical. If you enrolled everybody with apnea or obstructive apnea, I think you're not

likely to find an effect. I think you have to identify patients who got lots of apnea, unresponsive to conventional therapy, and who also have demonstrated reflux, whether it's acidic or non-acidic by one of those measures of analyzing it.

So just to give you one example of this issue with populations, and this is perhaps stating the obvious, but sometimes it's useful. We went through about 15 years ago lots of studies on serfactin and pre-term infants, and the primary endpoint there was intact cardiorespiratory survival, that is, that the hypothesis was the surfactant would improve the incidence of baby surviving without chronic lung disease.

Everyone thought that if the surfactant diminished the acute respiratory disease, the babies would clearly have less chronic lung disease. But we found out the hard way that that was wrong, that the chronic lung disease by and large is a developmental phenomenon that is minimally influenced by early lung disease.

The risk factors, I think, from chronic

lung disease are gestational age. Suppose for a minute that air leak babies is another risk factor that' important. We know that serfactin decreases air leak substantially. You can prove that it decreases from 20 percent to ten percent with a population size of 400.

All right. If you chronic lung disease among kids with air leak is 75 percent instead of 50 percent, and your reduction in air leak from 20 percent to ten percent reduces that risk to 50 percent, then your chronic lung disease -- this is a typo -- actually in that population goes down from 55 to 50 percent in the whole population, taking all comers, and to identify that with statistical certainty, you need thousands of babies to study.

All right. The population that would be amenable or would respond to the surfactant in terms of decrease in chronic lung disease is a small portion of the overall population of premature babies. So you need lots and lots of babies to study.

Now, neonatology, again, just to sort of state some history. We're intense with this. We into

instant gratification. We like to get on the bandwagon. If there's a new treatment out there we use it. Usually there's no investigation or little investigation, no due process.

It may get to be a standard practice, as has happened with metoclopramide, as happened with cisapride, without there being any evidence of efficacy and with, in fact, in some of these circumstances there being significant safety issues that arose later.

And then finally some cooler heads prevail and go back and do the studies that show is there or is there not efficacy or safety.

And I can put up the list here of things that have been studied, I think, relatively poorly, where we've sort of learned again and again from the history that therapies are not benign, and most recently with the steroid phenomenon, we've gone from using steroids in 80 percent of babies less than 1,000 grams to very, very infrequently because of the neurodevelopmental follow-up data that has come out on that population that suggests that those babies have

increased cerebral palsy and other significant neurological problems.

And, of course, this sort of applies to intensivists of all sorts, but it's good to keep in mind.

Now, for PPIs, just a few points. I think reading the literature there is no evidence that gastroesophageal reflux in pre-term babies, in healthy pre-term babies, that is, babies who don't have accompanying chronic lung disease, neurological problems, and so forth, all right, is any different in its outcome than the same reflux in healthy term babies. So the question is: why would you even want to treat it?

There is no evidence that acid gastroesophageal reflux produces more frequent or more severe either esophageal or super esophageal symptoms than non acidic reflux. The studies haven't been done. No one has looked at that sort of simultaneously.

And there is very little evidence that some of the anti-reflux medications that we use now,

ranitidine and metoclopramide, really affect any of the super esophageal symptoms in pre-term babies. Very little evidence, indeed.

And so when we look at these trials in pre-term infants, I think selecting clinically relevant efficacy endpoints is important. I mean, I would suggest sometimes the simpler the better in these things.

I think at the bedside, anyway, our primary issues are significant apneas, bradycardias, and desaturations, and the types of interventions they need from the nursing staff. So a baby who needs to be bagged vigorously, that's a significant complication.

Documenting reflux or reflux episodes by pH probe in an asymptomatic baby is not a very significant endpoint.

On the other hand, I think it's important if you study these agents, you need to look at reflux to start with and reflux to end with and see if you have any effect and see if you have any change of symptoms.

Secondary endpoints in these kids, clearly less hospital stay would be an issue because a lot of these kids stay in the hospital for prolonged apnea. Whether this might affect the use of home monitors, and whether it might alter their profile of discharge medications, other agents that they might not have to have if they're on a successful anti-reflux medication.

In terms of safety, the things are growth. Infection is an important one because suppression of gastric acid may have some ramifications in terms of gastrointestinal flora, intestinal infections, and whatnot.

Feeding tolerance, liver function with the PPIs in pre-term infants is probably important to look at.

Various drug interactions with other prokinetic agents, and so forth, and a two-year neurodevelopment outcome.

Careful selection of the study population I alluded to is critical, and then, of course, the study decision. I think Dr. Wilfond is going to talk

about that some, but I think what's proposed in the WR is a randomized withdrawal study, and I would be interested in hearing everybody's thoughts about that study versus traditional placebo controlled, which in my mind has a number of positive points associated with it.

So I think I'll end there. Thank you.

CHAIRPERSON CHESNEY: Thank you very much, Dr. Hudak. It clarified a number of issues for me.

Our next speak is Dr. Wilfond, who's going to discuss the ethical issues of using randomized placebo controlled withdrawal trial design in pediatrics. And I understand he has a Macintosh presentation that may take a few minutes to set up. Is that still correct?

While we're waiting, although --

MR. WILFOND: Where's the microphone.

While the slides are going on, I can actually begin my talk just to sort of move us along.

CHAIRPERSON CHESNEY: Thank you.

MR. WILFOND: I'll just probably step over a moment to adjust something as the time comes up.

It's a pleasure to be here. One of the things that I was struck by listening to the last talk was the realization that as a pulmonologist who takes care of these children after they go home from the nursery, that reflux meds. are the least of our problems.

We also have enormous confusion on how to use the monitors themselves, and even worse than the reflux meds. is the use of diuretics, which an abysmal sense of confusion. So I really applaud this group for tackling this issue because I think it is a very important issue.

The first slide that I'll show you in a moment will describe the six major issues that IRBs are tasked to look at when they consider research, and what I'm going to do today during my talk is to try to take the issue of placebo controlled trials and try to refine it down to what I consider to be the essential concern or the essential issue based upon walking you through the regulations and how the regulations apply to pediatric trials.

It look like I'm about to come on. I guess

not. But anyway, the == I keep on thinking it's about to happen, and then it's getting slow.

Essentially the general regulations for research include six main criteria, and the first three criteria have to do with the balancing of risk and benefits, and clearly, that's where the issues of placebos come around, trying to not expose children to unnecessary risks and to maximize safety.

Okay. There you go. I think I can talk pretty loudly.

So this was the slide I meant to show you before. Just the first three regarded the issues of safety and benefits.

But for the pediatric regulations though, we have a little more of a complicated design, but where's the little pointer?

And so for pediatric regulations, we tend to actually ask a series of questions to try and decide how to assess the research, and the first question has to do with whether there's a prospect of direct benefit or no prospect of direct benefit.

And in addition to that categorization, we

have to decide how much risk there is and the categorizations of risk are minimal risk, a minor increase over minimal risk, or a greater than moderate increased risk over minimal risk. You can see these are sort of hard to be clear exactly what they mean with that alone.

But the importance of this categorization is that based upon which category it is, there are additional considerations to address. So if there is a prospect of direct benefit, then we have to ask the question about whether the risks are justified by the benefits, and whether or not that ratio is as favorable as the alternatives.

However, if there's no prospect of direct benefit, then we have to look at whether the risks represent commensurate experience and whether it provides vital knowledge about the subject's disorder.

And certainly I think this is an area where there's no question that I think this is a very important issue.

So the first question that we have to decide if we want to consider how to look at a placebo

controlled trial, such as the ones we're considering here, is how to categorize that trial within those regulations.

And the first challenge is whether we apply those risk categories to the entire study or to the individual component. So do we ask the question: should this entire trial be no prospect of direct benefit or do we look at specific components?

And by specific components, I mean, you know, if we're doing pH probes, proton pump inhibitors, the placebo, the blood draws, do we look at each of these as a group or do we look at them separately?

And the problem of looking at them as a group, is that then the benefits of one could justify the risks of the other. So we thought, for example, that there was great benefit to looking at PPIs. In theory one could then justify doing liver biopsies on children.

And so, you know, I think intuitively we have a sense that that perhaps is not the way we ought to be doing things. It's perhaps better to look at

things as individual components.

So the question we have to then ask is: how should the placebo arm itself be considered?

And before I get into that analysis, I want to give you some what I would describe as intuitions about placebos. I think we all have a sense that placebos are not acceptable, particularly if there's an effective intervention to avoid significant morbidity and mortality.

So, you know, we wouldn't use placebo controlled trials for leukemia, for meningitis, for status epilepticus, for status asthmaticus. These are serious enough diseases for which there are interventions, although not always effective, that we would not consider putting a person on a placebo and not active treatment.

However, there are many groups that have looked at the question of placebos and tried to identify when are placebos appropriate, and the examples I'm going to give are fairly familiar. These are from the American Academy of Pediatrics, '95, Committee on Drugs, and they suggest that when there's

no commonly accepted therapy, if the commonly used therapies has questionable efficacy, if the commonly used therapy has significant side effects, the disease has spontaneous exacerbations or remissions, or the placebo is an add-on to established therapies. So these are the general types of reasons that we think the placebos are acceptable.

So what I want to do is to try to take these reasons and try to place them within the regulations as it relates to our trial. So in order to look at the risks and benefits of the placebo arm, we have to clarify what would happen without the trial, and that's necessary to assess the relative risks and benefits because we have to assess them compared to some baseline.

And so the first question we have to ask in terms of that baseline is whether or not the placebo arm offers a prospect of direct benefit compared to that standard alternative, and if that's the case, then we would look at it under the regulations of 405.

However, if we think it does not offer a

prospect of direct benefit, then we have to consider whether or not the placebo arm poses more than minimal risk or is more than a minor increase over minimal risk.

If it was more than a minor increase, then the approval process would be much more complicated. So I'm going to make an assumption that when we look at this trial we're going to be looking at it either under 405 or 406.

So I think the main issue though is summarized by the last speaker, is that, you know, the standard treatment is to use a range of anti-reflux meds., but as was described, that the efficacy and the value of these is uncertain, although the good news is that the risk of these drugs that are currently on the market is relatively modest.

However, I think it would be hard to make the claim, at least in my view, that putting people on placebos offers them a prospect of direct benefit compared to what they otherwise would be getting with treatment.

So the question we have to ask is whether

the risks of the placebo arm are more than a minor increase over minimal risk.

Now, I think what's rally key here, and I'm going to go through the two studies briefly, is that the Study No. 2 is taking people who are being monitored and where there are interventions available for apnea. So to the extent that our endpoint is apnea, these are people who are in a very carefully monitored setting.

So, you know, putting somebody on placebo in that setting, I think, would have less risk than if they were in an unmonitored setting.

And, again, I think it was discussed before, the whole approach of withdrawal of patients who are having concerning symptoms provides another safety way of trying to minimize the harms.

In the Study No. 4, which were the infants from one to four -- 11 months of age, rather, they exclude children with ALTs, which I think is probably a good thing because those are the patients who would have had the most to lose by being placed on a placebo.

However, it's complicated, and I have to admit this is where I'm a little in my own mind unclear what to do for two reasons. One is that those are precisely the sorts of kids that we are most interested in treating.

But an additional challenge though is how do we define an ALTE because, again, seeing this in the hospital, you know, many parents will say, "My child stopped breathing."

And you ask them for how long, and they will say an hour. And you know that's not really what happened, and you have to really sort of walk back and try to sort out what was going on.

So I think the issue of out-patient ALTEs and how they're categorized and how people are excluded on that basis.

So ultimately, the question about whether the risk of being a placebo arm under these conditions is more than a minor increase under minimal risk I think can boil back up to the three questions.

One is whether there's any unnecessary risk that can be further identified, whether that risk

can be minimized, and whether having a DMC as has been suggested in the written request will help that also.

So I think that in the end whether it's no more than a minor increase is based upon a judgment that what we expect will happen in children in the placebo group.

And I think as long as under the described conditions, and clearly, they need to be articulated with a little more. So I'm really talking more on general principles, but I think under the described conditions particularly in terms of people being monitored, excluding ALTs, having a withdrawal program, that reflux in both groups would not be expected to cause significant harm to the children in comparison to children in the active treatment groups.

And I think because of that, I think the placebo arm does not pose a greater than minor increase over minimum risk to these children. So this is my quick reading of this, and I'll be interested to hear what people have to say, but I think the main point I want to make is that I don't think that placebo controlled trials in this population are

necessarily ethically problematic as long as they're done appropriately.

I'm done.

CHAIRPERSON CHESNEY: Thank you very much, Dr. Wilfond.

We were scheduled for an open public hearing at 9:15. So I think we need to ask if there is anybody that wants to speak to this issue.

DR. PEREZ: We have two open public hearing people. First I'd like to recognize Dr. Gardener.

DR. GARDENER: Good morning. My name is Jerry Gardener, and I'm with Science for Organizations, a scientific consulting company that works with pharmaceutical and biotechnology companies, and I'm here representing Science for Organizations.

The main point I'd like to make is to suggest to the committee that they consider emphasizing the effect of proton pump inhibitor on gastric and esophageal pH instead of emphasizing the pharmacokinetic measurements.

This slide summarizes my background and

experience. I served as Chief of the Digestive Disease Branch of the National Institutes of Health and held the IND for omeprazole when it first became available.

If you could, go back one.

I held the IND for omeprazole when it first became available for human use. I've designed, conducted, and analyzed results from studies with a number of proton pump inhibitors, as well as histamine H_2 receptor antagonists, and I've analyzed data from over 1,000 gastric and esophageal pH recordings.

Next slide.

This slide summarizes the reasons that I'm suggesting that you emphasize the effect of proton pump inhibitors on gastric and esophageal pH instead of the pharmacokinetics of proton pump inhibitors.

First, there's no correlation between pharmacokinetic parameters and effects of the drug on gastric or esophageal pH.

Second, the effect of the drug on gastric and esophageal pH reflects the action that leads to clinical efficacy.

And, third, measuring the effect of proton pump inhibitors on esophageal pH in GERD patients can confirm the diagnosis.

And finally, I think that pharmacokinetics should be assessed, but only in a limited way.

This slide illustrates typical results from pharmacokinetic measurements and pH recordings with a proton pump inhibitor. The data given in the left panel are medians from 26 healthy adult subjects, and in the middle and right panels are from 19 adult subjects with GERD.

The left panel shows the plasma concentration time curve for a proton pump inhibitor given just before breakfast, and as you can see, the plasma concentration peaks at approximately four hours, and then decreases, and there's no detectable drug in the circulation after ten hours.

The middle panel shows gastric acid concentration at each hour during a 24-hour recording period. The curve in blue was obtained at baseline, and the phasic decrease in acid concentration is caused by the ingestion of meals which buffer gastric

acid, and then this is followed by stimulation of acid secretion and a subsequent rise in gastric acid concentration.

The curve in prink was obtained after a single dose of a proton pump inhibitor just before breakfast. Three to four hours after dosing, there's a significant decrease in gastric acid, and this decrease persists for at least 24 hours. Thus, even though there's no detectable proton pump inhibitor in the circulation after ten hours, there's a persistent effect of the drug on gastric acid.

The right panel shows the esophageal acid concentration measured at the same time and then in the same patients as gastric acid in the middle panel.

The curve in blue was obtained at baseline, and the increase in esophageal acid concentration results from reflux of gastric acid into the esophagus during the post prandial period.

The curve in pink was obtained with a single dose of a proton pump inhibitor given just before breakfast, and you can see that the drug virtually abolished esophageal reflux in these

patients.

So, in conclusion, this slide illustrates that there's no correlation between the time course of action of a proton pump inhibitor and its pharmacokinetic time course.

Other analyses that I won't present show that there's no consistent correlation between any pharmacokinetic parameter and any measure of the effect of the drug on gastric or esophageal pH.

Thank you.

CHAIRPERSON CHESNEY: Thank you very much, Dr. Gardener, for clarifying that very important issue.

Our next speaker at the open public hearing i is Dr. Kerns from formerly the University of Arkansas. I'll let you introduce yourself now.

DR. KERNS: Thank you. I'm Greg Kerns. I'm Chief of Clinical Pharmacology at the Children's Mercy Hospital in Kansas City, Missouri, and Professor of Pediatrics and Pharmacology at the University of Missouri at Kansas City.

My comments admittedly are somewhat

spontaneous, hopefully will be considered, and I first want to declare publicly that I have been a consultant and an investigator for many companies that study acid modifying drugs in children, which includes Merck, Reliant Pharmaceuticals, Wyeth Ayerst, Santarus, and pretty much if they made one, I probably talked to them.

I also need to disclose publicly that I am also a consultant to the Food and Drug Administration. So if anybody is totally conflicted, I guess that would be me.

I want commend the Advisory Committee for having this hearing, and particularly with respect to taking on this topic. I think we've all heard this morning a variety of things from how to do it, how not to do it, how should we do it, how much we do it, and perhaps just recently, perhaps we shouldn't do anything, as was mentioned.

I don't know that my view is the same. I think I can break my comments down into three areas: what we must do, what we should do, and then issues about what we can do.

First, what we must do. From the '94 pediatric rule through the '98 rule to the Best Pharmaceuticals for Children's Act, everyone agrees that what we must do is to make information that will let use drugs in children better.

It's like the recent alignment of the planets if you've watched things in the evening where you have a wonderful -- for those astronomers like Ben Gold. Rarely do we have such concurrence about what we must do. The will of the Congress is clear, and the will of the agency is clear, and the will of the investigators.

Then the issue of what we should do to me really represents an incredible conundrum, and I pick that word intentionally, because there is not agreement with regard to this particular therapeutic category and many others what we should do.

I think there are some things we can follow. We should do things that are responsive to the needs of the patients and responsive to the needs of their families and responsive to the needs of the physicians and the other health care professionals

that are charged with providing day in and day out care to these children.

Therapy has to be linked with knowledge, and hopefully that knowledge will give us guidance on how to use, when to use, and when not to use.

And some of the success stories that have been part of the pediatric initiative are clear with the implications on labeling of some drugs that we have actually learned we probably shouldn't use.

Other than being responsive, we have to be responsible in what we do. There are issues, ethical issues, that are very concerning, and I'm speaking now as an investigator concerning as we present these studies to parents and children to solicit their participation.

I would argue that as a partner and as an advocate for children, convincing someone to be part of an admittedly underpowered study to assess efficacy, but rather to ask questions about clinical utility poses little advantage, little incentive to subject the child or their family to the rigors of an investigation where the answers may well be known.

It's critical that we be responsible in using the information that we have. It seems that every day we wake up and look at a new proposal to study a new compound. It's like deja vu al over again. And I wonder many times is it really necessary.

Do we utilize the information that we learn in the next study as opposed to creating a grand crescendo that makes each and every study more onerous, more difficult, and unnecessarily more risky than the one before. We have to take care and caution with that.

And lastly, what we should do, it's clear that we have to do things that are reasonable, and Dr. Hassall made excellent points in his discussion about doing things that are reasonable and realistic and will answer the questions.

The last thing I wanted to comment on is the issue of what we can do. We're in a wonderful time in pediatric clinical pharmacology where we have tools at our disposal that many of us spent years developing, and more years dreaming about.

Dr. Spielberg has on many occasions talked about the importance of understanding the association between the ontogeny of drug metabolism and physiology and linking that together to make responsible studies and study designs.

I think we have to heed that prudent advice and even turn it into a warning so that as we make study designs of drugs like this, we're not forgetting the things that are there for us. The fruit doesn't always have to hang at the top of the tree, and because of the expense and energy, we have to be wise in making sure that the harvest targets the intended population.

What we can't do is engage into some process of documenting clinical utility in the hopes that we'll answer perhaps an interesting question. At the end of the day children and their parents and their doctors are only going to be served by the kind of rigorous inquiry that answers to questions that are critical to making treatment decisions. That is not the abrogate the responsibility of regulators.

We have the best system in the world in

the United States, but by putting things together, we can do it right.

And lastly, let me mention one thing that I hope the committee will consider. On April 1st, a draft guidance was published by FDA on exposure response relationships. If you've not read that guidance, I would argue all of you to read it.

This guidance is truly -- and I don't say this with any lack of sincerity -- a masterful work because it deals with the problem of identifying a target population and putting together the kinds of information that we just heard from Dr. Gardener to demonstrate that a drug has an effect that is or isn't related to its plasma concentrations.

And if that effect transcends all of the age groups, it's easy to define the dose, which at the end of the day every pediatrician, as they contemplate the drug, and we heard about the list of ten or 15 in neonatology, what's the neonatologist's first question? What's the dose?

So I hope you would consider that. I thank you for the opportunity to make these comments.

CHAIRPERSON CHESNEY: Thanks you, Dr. Kerns.

We'll try to remember the four Rs, responsive, responsible, reasonable, and realistic.

Are there any other speakers for the open public hearing?

(No response.)

CHAIRPERSON CHESNEY: Then what I would like to do if it's all right with our FDA folks is to take ten or 15 minutes to ask the committee and our invited consultants if they have questions of this morning's speakers.

No specific questions. So we'll take a -- I'm sorry. Dr. Fink.

DR. FINK: This is, I guess, a question for Dr. Wilfond.

In terms of a withdrawal trial, it would seem like a withdrawal study, although clearly ethical and feasible, would hide safety data. And has anyone designed a withdrawal trial where there is a control arm of non-diseased infants?

Particularly with proton pump inhibitors,

I guess my concern is taking away the acidic barrier to gastrointestinal infection. If you start with the trial design that puts all infants on the drug, how are you going to see if it causes adverse side effects?

DR. WILFOND: Well, as I understand, and I may have this incorrect, too, because it is a little confusing, I understand this withdrawal design means there's a run-in phase where they're on the drug, but then they're randomized to either the drug or placebo, and then based upon certain predefined criteria, they're withdrawn from the study.

I'm asking this to the other speakers because Gil Gray was asking me this question before, and I think we may be confused about what exactly the trial design is.

Is my description correct?

MR. HUDAK: Yes.

DR. WILFOND: Then if that's correct, then, again, it's actually very similar to many asthma trials where there's an initial period on the drug, but then half are taken off. So you would be able to

tell during that period of time whether there were any specific safety issues. Does that --

DR. FINK: Yeah, well, I don't know if that haws ever been applied like with asthma, where we're looking specifically at safety. Usually the safety trials are done first, and then you do a therapeutic or efficacy trial.

And I think it would mask safety if you run all infants in on the drug for a period of time.

CHAIRPERSON CHESNEY: Dr. Nelson.

DR. NELSON: I'd be interested in being corrected, but my understanding is that most of the safety data is generated by the description of the frequency of events within the population on the drug, and that at least the placebo designed trials are not powered relative to safety considerations.

So that it's unclear to me that you would need a placebo arm for that purpose.

DR. BIRENBAUM: I just want to clarify the placebo controlled, randomized withdrawal trial design so that everyone is on the same page about it.

In fact, this trial design has bene

utilized multiple times in the past for the agency with asthma specifically as the condition being studied, and it was used because it was determined that there's a need for a placebo controlled arm, but exposing patients for prolonged periods, like three months, to placebo with a condition like asthma would be unacceptable.

So in such cases, all patients who are enrolled, eligible for enrollment into the study, are enrolled, and receive the treatment of study, the study drug; for a period of time that is determined would establish serum levels that would be correlated to some treatment effect, and after that time, if they continue to meet certain criteria, are then randomly assigned to either continued study treatment or placebo, and that is the period of drug assessment for both efficacy and safety, and it is usually of duration which the population is considered to demonstrate a long enough period of time for efficacy for which the study is powered and will hopefully unmask strong signals or any signals of safety.

But clearly, no study could ever be

powered to safety assessments in the short term. They're powered to efficacy assessments.

This trial or any randomized withdrawal trial which has a placebo arm is no different in its duration of randomized withdrawal for the placebo arm than it would have in a standard, simple, placebo controlled arm in which you have no run-in phase. It would be a trial of the same duration.

The one disadvantage of this trial design is that at the end of the day in terms of long-term follow-up, no patient in this study will have received no study drug treatment. So at the end of the day, all patients who are looked at from the long-term follow-up assessment will have received study drug.

CHAIRPERSON CHESNEY: Dr. Fink.

DR. FINK: Then I guess my question specifically with that design is for safety issues, why don't you also include a control group that is a non-disease, particularly in premature infants or neonates, a control group that is similar gestational age without GERD to look for -- to enhance your ability to detect safety signals.

DR. BIRENBAUM: It's an interesting point. However, confounders of that other arm may include whatever else might be the characteristics of that nontreated arm. So it might not be any different than looking at a historical control, except that the concurrent time period might be helpful.

But, yeah, that might be something to consider.

CHAIRPERSON CHESNEY: Are there any questions specifically directed for the speakers? Dr. Blackmon.

DR. BLACKMON: I wanted to clarify something with Dr. Wilfond because as I listened, it seemed to me the implication was that the active treatment arm didn't carry a risk, that your concern was with risks associated with placebo, and I'd just like you to speak to that.

DR. WILFOND: That's not what I meant. So I'm glad you clarified that. What I meant was by focusing on the placebo arm, I was trying to suggest that for the placebo arm where there was no specific prospect of benefit for those individuals, that then

the issues would be how great is the risk.

For the treatment arm, where there is a prospect of direct benefit, then it's an issue of just balancing the benefits with the risks. But I wasn't trying to address that question. I was really focusing more on the placebo group.

DR. BLACKMON: But, again, that implies that the only potential benefit is with the treatment, and if you truly have not committed that this treatment is the treatment of choice, then how can you infer that that's the only group that gets a chance at benefit?

DR. WILFOND: I think what you're getting at is that risk and benefits are two sides of the same coin, and you can describe benefits as negative risks or risks with a negative benefit.

And so you're right. It gets very complicated in terms of how you want to look at it, and I think you could look at it either way. But from the point of view of one way of trying to interpret the regulations is to say that, you know, the alternative to these kids also is not being in the

trial. Then they can do -- being in the placebo group itself doesn't offer them a benefit compared to if, for example, the parents wanted to not be in the trial and also not be on the drug. they could do that also.

So it's not clear that there's a specific benefit to be in the trial itself for that group.

DR. WARD: But if there is any adverse effect associated with the medication, the absence of that adverse effect it seems to me a benefit.

DR. WILFOND: I don't disagree with that. Again, it really is that issue of how do you choose to look at and define it, and I think that, one, I guess what I would say in spite of the analysis I presented, I also do think it would be feasible to -- actually in the few times I've tried this, regardless of which category of the regulations you use, you come out with the same answer. So it's not clear to me that you actually come up with different intuitions about what the appropriate decision is.

DR. BLACKMON: And the last point I'd like to make is that the discussion really hasn't dealt with the fact that there are non-medication

interventions that Dr. Hassall covered for us that aren't addressed in the protocol. So that the placebo arm does get the benefit of what we do know about other mechanisms for controlling reflux.

DR. WILFOND: Can I respond real quickly?

CHAIRPERSON CHESNEY: Is that a specific question for Dr. Wilfond?

DR. BIRENBAUM: I guess it's a general comment. In looking at the design and the discussions about the design, we haven't really addressed the non-medication component of management.

CHAIRPERSON CHESNEY: I agree.

Are there any other questions specifically for the speakers? And then we'll take a break. We've got many, many things to talk about.

Dr. Spielberg, you've had your hand up for a while.

DR. SPIELBERG: One more question with respect to randomized withdrawal. I think Dr. Birenbaum very nicely summarized the benefits of doing this kind of design from a safety point of view.

There's also a potential benefit from an

efficacy point of view, Bob Temple's in Richmond idea where you look for patients, particularly for difficult to evaluate conditions, and I would posit the GI disease is probably among the most difficult to evaluate the outcomes, where you have a run-in period on drug. You take patients who appear to respond.

You then randomize to withdrawal, placebo versus drug, to see if, in fact, that response truly is attributable to drug, with a relatively short period of time to maximize safety for the patient. So there is potential benefit.

The question I have though is for randomized withdrawal designs, which I really like, it presupposes a degree of stability of process over time, and one of the things we're looking at here is a very fluid population where maturation of all the processes that we're concerned about is going on very rapidly, but very differently among different kinds.

And so I do have some concern about this kind of design in a situation where you have that much variability because the Ns then go up dramatically to actually be able to demonstrate effect.

CHAIRPERSON CHESNEY: One more questions and then our break.

Dr. Gorman, you have your hand up earlier.

DR. GORMAN: This is a question for Dr. Hassall.

You mentioned a dramatic decrease in the amount of GI surgery with a specific regime, but I'm not sure I got the details of the regime, you know, that you were treating GE reflux disease in a way that decreased the number of interventions. Did that or did that not include the agents we are discussing today?

DR. HASSALL: Yeah, there are two aspects to that that I didn't go into, and I appreciate the question.

Basically there are two ways that we approach it. First of all, we work very closely with the surgeons, the gastroenterologists and the surgeons, and we have much more stringent criteria for selection of patients for surgery than we did in the past.

So I might send the patient to a surgeon

for surgery. The surgeon might come back to me with questions, "Did you do this? Did you do that?" which is not something that happens in a lot of institutions.

The second aspect is yes, and the main point that you are bringing out is that, yes, since I started using PBIs in children about 1989, 1990, around then, and we published the first study in 1993 on a group of 15 children who were refractory to all other measures. Their parents wouldn't let us take them off drug so dramatic was their response.

Since then we've learned how PPIs can be used judiciously, how in some cases reflux may be transient, may be delayed gastric emptying from post viral infection or whatever, but we make patients early surgery or long-term PPIs.

We withdraw PPIs. We see if they relapse. We withdraw PPIs later, et cetera, et cetera.

So it's a combination basically of better selection for patients -- of patients for surgery or PPIs and the use of PPIs in adequate dosage itself.

CHAIRPERSON CHESNEY: Thank you.