DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING

TOPIC: REGULATORY UPDATE FROM

THE DIVISION OF ANTIVIRAL DRUG PRODUCTS, CDER, FDA

OPEN SESSION

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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. HAMMER: This session this morning is going to deal with a regulatory update from the Division of Antiviral Products. To start, I would like to have the individuals around the table introduce themselves for the record.

DR. MURPHY: I am Diane Murphy, Office Director for Office of Drug Evaluation IV.

DR. JOLSON: I am Heidi Jolson, Division Director for Antiviral Drug Products.

DR. BIRNKRANT: Debbie Birnkrant, Deputy Division Director, Antiviral Drug Products.

MS. MASCIALE: Andrea Masciale from the Regulatory Policy Staff of CDER.

DR. MURRAY: Jeff Murray, Medical Officer at Antiviral Drug Products.

DR. LIPSKY: Jim Lipsky, Director, Clinical Pharmacology, Mayo Clinic, Rochester, Minnesota.

DR. POMERANTZ: Roger Pomerantz. I am the Chief of ID and Professor of Medicine at Thomas Jefferson University in Philadelphia.

MS. STOVER: Rhonda Stover, FDA, Executive Secretary for this committee.

DR. HAMMER: Scott Hammer from the Beth Israel Deaconess Medical Center and Harvard Medical School in Boston.

DR. EL-SADR: Wafaa El-Sadr, Harlem Hospital and Columbia University, New York.

DR. FEINBERG: Judith Feinberg, University of Cincinnati.

DR. HAMILTON: I am John Hamilton, Chief of the Division of Infectious Diseases and International Health at Duke University.

DR. HAMMER: Thank you. There will be a couple of other members coming a bit late.

I would like to turn now to Rhonda Stover who will read the conflict of interest statement

Conflict of Interest Statement

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The focus of this meeting is to discuss regulatory issues. Since no questions will be addressed to the committee by the agency on issues dealing with a specific product or firm, it has been determined that all interest in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting when evaluated against the agenda.

DR. HAMMER: Thank you.

I would like to turn now to Dr. Heidi Jolson.

Welcoming Remarks

DR. JOLSON: Good morning. We are pleased to welcome you to this special session. This should be a session that will be relaxing for you. No votes will be taken on any of the material that is presented today, in fact, Congress has already done that for you, so you can just kind of relax, try to absorb some of the information that is presented, and we will be happy to discuss any of it with you, clarify anything, and answer any questions.

You should know that this committee was actually the first committee to provide regular updates to its

members, and because of the success of these regular updates, the Center has now requested that all committees, all advisory committees receive some sort of annual updates.

At this time, we have interpreted that to include regulatory updates because there have been so many changes in the past year or so at FDA, and we wanted to make certain that you, as committee members, were aware of some of the new regulatory initiatives at the agency.

So, the purpose of this morning's session will be to provide an update on some of these newer regulatory initiatives both within the agency and also within the Division of Antiviral Drug Products.

I think you will appreciate after this morning's session that this is really a time of great regulatory change in the agency, and this is really exciting for us at FDA, and we look at this as really a very positive process, because we believe that these regulatory initiatives will both encourage innovation through their implementation and also improve the overall drug approval and development process.

As you will hear, several of these initiatives are

going to encourage drug development for special populations or populations that are in need of therapies in a more expedited manner. This is challenging for us as FDA staff. We need to keep abreast obviously of both scientific and clinical changes, but also, as you will appreciate this morning, a lot of new regulatory changes.

So, this morning, we would like to share with you some of these changes, so that you will be aware of the regulatory climate that we do our work.

Moderating this morning's session will be Dr. Debra Birnkrant, Deputy Director of the Division of Antiviral Drug Products, and she will provide an overview of this morning's agenda and moderate the session.

So, Debbie, I will turn the meeting over to you.

Introductory Remarks

DR. BIRNKRANT: Good morning. As Heidi said, the purpose of this morning's open session is to provide a regulatory update to our advisory committee, and this morning we will cover four areas of interest to the committee.

The first part of the morning will focus on FDA's

Modernization Act of 1997, and our first speaker is Ms. Andrea Masciale of CDER's Regulatory Policy Staff, who will provide an overview and comment specifically on fast track designation, expanded access, dissemination of information on unapproved uses of drug products, the evidence standard, the Prescription Drug User Fee Act, Part 2, or PDUFA-2, and issues related specifically to the advisory committee.

FDA's pediatric initiatives will be presented by Dr. Therese Cvetkovich.

After our break, Dr. Murray will focus his comments on requirements for accelerated and traditional approval for new therapies to treat HIV. His comments will address the use of HIV-RNA for the determination of endpoints in clinical trials to support marketing applications as a follow-up to our discussion with the committee last year.

Dr. Toni Piazza-Hepp, of the Division of Pharmacovigilance and Epidemiology, will conclude FDA's presentation this morning with a discussion on post-marketing surveillance of antiviral drug products. As an example, she will present the findings from our adverse

event reporting system for the currently marketed protease inhibitors.

This will be followed by an open public hearing. Questions will be taken after each speaker concludes.

Without further ado, I would like to introduce Ms. Andrea Masciale of the Regulatory Policy Staff.

FDA's Modernization Act (FDAMA)

MS. MASCIALE: Good morning. It is a pleasure to be here this morning to talk with you about the Food and Drug Administration Modernization Act of 1997.

[Slide.]

The Modernization Act incorporates the most sweeping changes to the Federal Food, Drug, and Cosmetic Act in 35 years. The original piece of legislation introduced by Senator Kasselbaum evolved considerably over a three-year process and eventually was passed by Congress and signed by President Clinton on November 21, 1997.

The Modernization Act codifies many programs already in existence in CDER and some FDA Reinventing Government initiatives. The Modernization Act went into effect in February 1998. FDA has made a public commitment

to implement the provisions of the Modernization Act in a timely manner while also attending to other responsibilities under the Food, Drug, and Cosmetic Act.

[Slide.]

Implementing the Modernization Act requires the agency to issue over 100 documents. These documents include regulations, guidance documents, various Federal Register notices, and reports.

Where the statute specifically requires rulemaking, the agency is issuing regulations. Regulations are binding requirements that have the force of law, and they are proposed and later finalized in the Federal Register with adequate time for public comment in between publications. When we have determined that new regulations or changes in existing regulations are not necessary to implement the Modernization Act, implementation usually takes the form of a guidance document.

Guidance documents are developed under the agency's Good Guidance Practices, and are informal agency statements that are not binding on FDA or on the public. They state the agency's current thinking on the subject of

the guidance, but other approaches may be used if they satisfy applicable statutes, regulations, or both.

Each significant or Level 1 guidance document is published on the CDER home page, and is the subject of a Notice of Availability in the Federal Register, which includes addresses for interested persons to obtain copies of the document.

[Slide.]

For the balance of my talk, I am going to cover some of the provisions of the Modernization Act that may be of interest to this advisory committee. The reauthorization of the Prescription Drug User Fee Act of 1992, dissemination of information on off-label uses, fast track, the evidence standard, expanded access, Phase IV studies, and sections affecting advisory committees including scientific advisory panels and dispute resolution.

Following my presentation, Dr. Cvetkovich will discuss the provisions of the Modernization Act that deal with studying drugs in the pediatric population.

[Slide.]

I would first like to address the reauthorization

of the Prescription Drug User Fee Act, which we call PDUFA. As you recall, PDUFA was first passed in 1992 when, in exchange for receiving user fees in connection with certain human drug applications, FDA agreed to a five-year program of annual performance goals for application review.

In November '97, as part of the Modernization Act, PDUFA was reauthorized for five more years with performance goals aimed at slightly reducing review times, but focusing more on reducing drug development times.

PDUFA-2 provides for more money to achieve these enhanced goals in terms of higher fees and a workload adjustment. The PDUFA-2 performance goals are expected to reduce review time slightly, and will be phased in over the next five years. The goals are 10 months for standard applications and efficacy supplements, down from 12 months, and 4 months for manufacturing supplements, down from 6 months.

Priority application reviews are still set at 6 months. They did not changed under PDUFA-2.

[Slide.]

Other new performance goals are aimed at reducing

drug development times. These new goals include those from meeting management, clinical holds, dispute resolution, special protocol assessment and agreement, and paperless receipt and processing of submissions.

[Slide.]

On June 8, FDA proposed rules implementing Section 401 of the Modernization Act and allowing greater flexibility for manufacturers to disseminate information from studies published in peer-reviewed scientific journals about the safety, effectiveness, or benefits of off-label uses for approved drugs. This information must be both reliable and balanced, and can be disseminated for off-label uses which have been or will be studies and submitted to FDA for approval.

Under the Modernization Act and the proposed regulations, this information may be provided to help care practitioners, pharmacy benefit managers, health insurance insurers, group health plans, and federal and state agencies.

Dissemination of this information is tied to a commitment on the part of the manufacturer to do the

necessary research on the new uses. Generally, in order to disseminate this off-label information, the manufacturer needs to have submitted a supplement to the agency for the new use, or needs to submit time lines for completion of the studies and submission of the supplement to the agency. Firms or sponsors no longer would have to wait for FDA approval of a supplemental application before disseminating this information about unapproved uses of their products.

At least 60 days prior to dissemination, a manufacturer would have to submit to FDA a copy of the information to be disseminated and other data that is specified in the proposed rule. If FDA determines that the information is not objective or balanced, it can require the manufacturer to include additional objective and scientifically sound information or an objective statement written by FDA about the safety or effectiveness of the new use.

Manufacturers would have an ongoing responsibility to provide FDA with additional information about the disseminated new use, and the FDA could order the cessation of the information if the additional information indicated

that the off-label use may not be effective or may pose a significant risk to public health. FDA will reassess its proposed rule in response to comments and should issue a final rule before November 21st.

[Slide.]

Another provision of the Modernization Act that may be of interest to you is the so-called fast track provision or Section 112. This provision requires FDA to develop procedures to facilitate the development and expedite review of drugs that are intended for the treatment of a serious or life-threatening condition and that demonstrate the potential to address an unmet medical need. This section of the statute essentially codifies our accelerated approval regulations and gives the agency authority to accept and begin review of portions of an application before the entire NDA is submitted to the agency. CDER has already received requests for a designation as fast track products, and has made decisions on those requests within the 60-day time frame established in the statute. Currently, the agency is developing guidance on how we will designate a fast track product and

how we will handle reviews of such products once designated. As required by the Modernization Act, this guidance will be issued by November 21st.

[Slide.]

An important step, on May 15th we issued a guidance for industry entitled, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." In this guidance document, the agency articulates its current thinking on the quantitative and qualitative standards for demonstrating effectiveness of drugs in new drug applications and supplemental applications.

A draft of this guidance document had been previously published in draft for comment in March of 1997, and had stated FDA's interpretation of the requirement for substantial evidence under the Food, Drug, and Cosmetic Act.

In Section 115 of the Modernization Act, Congress confirmed FDA's interpretation as stated in the draft guidance by making it clear that the agency may consider data from one adequate and well-controlled clinical investigation and confirmatory evidence to constitute substantial evidence if FDA determines that such data and

evidence are sufficient to establish effectiveness.

[Slide.]

The Modernization Act codifies several programs to provide patient access to experimental therapies. Section 113 sets up a publicly accessible data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions.

The data base needs to be in a form that is readily understandable to the public and will include the purpose of the drug, the eligibility criteria for enrollment in the trial, the location of the trial sites, and a point of contact for enrolling in the trial.

A clinical trial will not be in the public database if the disclosure of such information would substantially interfere with the timely enrollment of subjects in the investigation. This database is being created by NIH in consultation with FDA.

Section 402 of the Modernization Act essentially codifies FDA's current regulations in 21 CFR Part 312 regarding treatment INDs and emergency IND procedures, which provide patient access to unapproved investigational drugs

for serious diseases.

[Slide.]

One of the provisions of the Modernization Act that was of particular interest to consumer groups during the development of the legislation was Section 130 concerning reports of post-marketing approval studies or Phase IV studies. This provision requires FDA to develop regulations requiring annual progress reports on the status of Phase IV studies from sponsors who have entered into agreements with the agency to conduct these post-marketing studies.

In addition, FDA is to published a unified annual report in the Federal Register on the status of the studies and on the status of the agency's reviews of the studies. The agency is currently developing these regulations and procedures that are needed to implement this section of the Act.

[Slide.]

Section 120 of the Modernization Act called "Scientific Advisory Panels," includes provisions for CDER's use of advisory committees, like your own, that provide

scientific advice and recommendations regarding the clinical investigation of drugs and the approval for marketing of drugs.

Under this section, new advisory committees are to include representation of consumer patient interests, representation of interests of the drug manufacturing industry, and specialists with expertise in the particular disease or condition for which the drug under consideration is proposed to be indicated.

Under Section 120, FDA is to schedule advisory committee meetings, so that any matter for consideration by the committee may be reviewed within 60 calendar days of its being ready for review.

Furthermore, the agency is to notify affected persons of the agency's decisions on advisory committee recommendations within 90 calendar days of the committee recommendation.

Section 120 also contains provisions for new conflict of interest considerations for members of advisory committees and education and training for new advisory committee members. The agency is about to issue a guidance

document explaining how it will implement this section of the statute, which will supplement the policy and guidance handbook for FDA advisory committees.

[Slide.]

FDA recently issues a direct final rule to implement Section 404 of the Modernization Act by amending the agency's procedural regulations to allow sponsors, applicants, and manufacturers of drugs or devices to request advisory committee review of scientific controversies. This rule will become final on October 29th unless the agency receives timely significant adverse comments.

Since sponsors and applicants of drug products already have the option of requesting advisory committee review of disputes under other CDER regulations, it is unlikely that this provision will have any impact on CDER advisory committees.

That concludes my prepared remarks. If you are interested in following the agency's implementation of these provisions, please check the CDER World Wide Web home page for any new information as it becomes available.

Thank you. I will take any questions.

DR. FEINBERG: In the slide entitled "Advisory Committees," what does it mean, the bottom part where it says, "Affected persons will be notified of the FDA's decision within 90 days"?

MS. MASCIALE: Affected persons would be the sponsor or the applicant of the drug product, the persons who would truly be affected by the FDA's decision on whatever matter the advisory committee considered.

DR. HAMMER: I have a question concerning the dissemination of information for off-label use. What type of monitoring is in place or is there any guidance for what monitoring should be in place by the agency for this activity?

MS. MASCIALE: I can say that we have issued the proposed rule and that the Commissioner's Office will probably issue a guidance document explaining it further or at least an internal policy document explaining it. Since it is still in its proposed stage, I don't know that any systems are already in place. They may be, I just don't know of any.

DR. HAMMER: Thank you.

DR. HAMILTON: Could I follow up on that, please.

What is the level of detail that is required in support of that kind of submission or that dissemination of information?

MS. MASCIALE: Level of detail in the information that can be submitted, I mean that can be disseminated?

DR. HAMILTON: The level of detail to support the disseminated information.

MS. MASCIALE: I don't know. It has to be in a peer-reviewed scientific journal, but I do not know what beyond that. It might be spelled out in the proposed rule.

DR. JOLSON: Andrea, can I help you out with that one?

MS. MASCIALE: Please.

DR. JOLSON: Remembering that none of this has been finalized because it is just in the proposed rule right now and has to go through rulemaking, what was proposed is that sponsors could distribute scientifically sound peer-reviewed publications providing that those publications provided enough information about the methodology of the study to support the conclusions that were being drawn.

That is what was proposed, and there were certain criteria in the proposed rule regarding the detail of the methodology that would have to be there that would allow a reader to reasonably conclude that the study was scientifically sound and the author's conclusions would be supported by the methodology. That is what is currently proposed and is open for public comment.

DR. EL-SADR: I have a question about another representation of the advisory committee, interests of the drug manufacturing industry. What is the intent?

MS. MASCIALE: What is the intent?

DR. EL-SADR: Yes.

MS. MASCIALE: The intent is to have another voice on the committee.

DR. EL-SADR: That would be adding to current?

MS. MASCIALE: Yes, over time we will be adding to current advisory committees, and it is basically a representation on the advisory committee. Voting would be an entirely separate issue.

DR. HAMMER: Dr. Hamilton.

DR. HAMILTON: I have a further question about

Phase IV studies. Are those reports or the results of Phase IV post-marketing studies routinely passed through this committee, one, and two, can this committee recommend that post-marketing studies must be done or must they be done in any case?

DR. JOLSON: We are going to discuss this a little later on because the committee should be aware of this distinction between post-marketing studies that are done under Subpart H, which is for accelerated approval. Those are the studies that are designed to provide confirmatory evidence of clinical benefit -- and Jeff Murray is going to be discussing that -- versus routine Phase IV commitments, and those could be any type of post-marketing study that needs to be done to provide further either dosing information, information in a special population.

As Dr. Murray is going to discuss, those studies are not absolute requirements. They are voluntary agreements on the part of the sponsor. In the legislation, my understanding is that it would include any Phase IV study, but for the committee's purposes, it would be important to distinguish your interest in the studies that

are done for traditional approval, that provide confirmation of clinical benefit versus studies that are done which could be either clinical or preclinical studies as part of voluntary commitments on the part of the sponsor.

I don't know if that helps or if that is a point of confusion.

MS. MASCIALE: I also should note that the agency is still creating proposed regulations about trying to implement this section, so when the proposed rule comes out, it should give a lot more information, and it should really clarify what studies we are talking about and what studies will come under this section of the Act and which won't.

DR. JOLSON: I think part of the issue here is that over the years, as drugs are approved, that have regular traditional approval, there are often kind of a laundry list of Phase IV commitments, and it really depends on the drug and the issues and how complete the new drug application was, and I think that someone, you know, finally said, well, what is FDA doing to see that these commitments are actually done and if they are done or if they checked off somewhere, and what happens to this information, and it

would be good to have a way of tracking that.

I think that the legislation is an attempt to make us systematically look at Phase IV commitments in terms of what we are asking for, and to make certain that when we ask for it, we are aware that the data comes in and that the question has been answered and it translates into labeling if that was the intent, because from the industry perspective, there is a lot of effort that goes into conducting these studies, and it is just a way of making certain that the agency's followup is appropriate for them.

DR. HAMMER: Dr. Lipsky.

DR. LIPSKY: Related to the issue of the off-label use, does that just include articles, or can, under that, the industry do direct to consumer advertising?

MS. MASCIALE: The section of the statute is pretty limited, and the proposed rule is, as well. It is to the particular people that I mentioned before, people in the health care industry, and it is articles from peer-reviewed scientific journals. It is pretty limited.

DR. LIPSKY: But could you have an ad that there is a new exciting development about, you know, product X,

contact your doctor?

MS. MASCIALE: No. You can't really say a universal thing like that because, you know, marketing firms can come up with some great ways of saying things, but, no, there is no allowance for direct to consumer in the provision.

DR. HAMMER: I may have missed this, but I have a question about the evidence standard. You outlined the new or the current evidence standard about one adequate and well-controlled clinical trial with supportive evidence being I guess the minimum requirement.

What was the previous evidence standard just for comparison?

MS. MASCIALE: Well, the previous was the statute said adequate and well-controlled trials.

DR. HAMMER: It was two for accelerated approval, but this is for routine.

MS. MASCIALE: We didn't really change it. What we did was when we interpreted it back in March of '97, we realized that the evolution of drug development, you know, there probably could be allowance for one with confirmatory

evidence, and then Congress came back and said yes.

DR. HAMMER: This may came up later, but does this then have implications for the confirmatory trials related to accelerated approval or should we defer that discussion?

DR. JOLSON: It really doesn't, at least right now, this isn't part of the equation. I think you can imagine that there are certain circumstances when one very large study may provide compelling evidence for certain indications in certain patient populations, and over time, the agency has recognized that maybe you don't always have to have two clinical studies.

I think that the two clinical studies came about at the time when clinical studies weren't as large or as multi-national and multi-center as they are now. So, in light of that, there are certain product areas, for example, in oral contraceptives where the interest is not in the number of studies, but is in the number of patient exposures and months of experience, and that could be captured perhaps in one extremely large clinical study that presumably involved many, many centers.

There are other areas where because either the

patient population is small or because the clinical studies are just so large and so representative of the patient population that one study is enough with additional support of information, but it is really product specific and indication specific in terms of where it is appropriate.

DR. HAMMER: Thank you.

DR. BIRNKRANT: Are there other questions for Ms. Masciale on the Modernization Act?

DR. MURPHY: Scott, I just wanted to also add to what Heidi was saying. I think the recognition of the fact that the goal here is consistency and replication, and with our multi-center trials, if one were to qualify a large multi-center trial, there are certain criteria that one would be looking at, which would be consistency within those centers, and also the robustness of the data, et cetera, before one would consider just that one trial.

DR. HAMMER: Thank you.

DR. BIRNKRANT: I think we may need to deviate from our planned schedule this morning -- but maybe not.

Our next speaker will be Dr. Therese Cvetkovich who, as she is getting ready, will provide an update for

pediatric initiatives. While she is getting ready, I would just like to follow up with something Dr. Hamilton brought up, about Phase IV commitments, not necessarily related to the Modernization Act, but just in general, and that is, when we do present an application to the committee, we are seeking advice and at times we turn that advice into requests for additional information from the pharmaceutical sponsors in the form of a Phase IV study, so we clearly look to you for that advice.

Pediatric Initiatives

DR. CVETKOVICH: I am very pleased to be able to present to you today some of the very important pediatric initiatives that are currently being undertaken by FDA.

[Slide.]

The absence of pediatric labeling information poses significant risks for children. Some of these risks include unexpected adverse events due to either specific age-related causes or overdose caused by lack of dosing information, undertreatment or dosing for the same reasons, and importantly, lack of access due to physician hesitance to prescribe medications in the face of insufficient safety

or dosing information.

[Slide.]

Lack of appropriate formulations may deny access to younger children when a liquid formulation that they can take is not available and may expose them to homemade formulations whether created by a mother at home or in the hospital, some of the formulations may have no information on their bioavailability and safety.

[Slide.]

In response to the well-documented deficiencies in pediatric use information and product labels, Congress included in FDAMA, Section 111, pertaining to the pediatric studies of drugs. Some of the important provisions of Section 111 include market exclusivity for new drug. This provision permits certain applications to obtain an additional six months of exclusivity if, in accordance with the requirements of the statute, the sponsor submits information relating to the use of the drug in the pediatric population.

A requirement that the FDA develop, prioritize, and publish a list of approved drugs, called "The List," for

which additional pediatric information may be produce health benefits in the pediatric population.

Approved drugs included on this list may qualify for an additional six months of market exclusivity provided that the sponsor submit pediatric use information in accordance with the requirements of the statute.

Finally, issuance of a report to Congress no later than January 1st, 2001, assessing the effectiveness of the program in improving information about important pediatric uses for approved drugs, the adequacy of the incentive, and the economic impact of the program on taxpayers and consumers.

[Slide.]

Some of the issues related to implementation of Section 111 of FDAMA include the following: first of all, its generation of "The List," preparation of a guidance for industry on qualifying for pediatric exclusivity, some of the activities of the Pediatric Formulations Working Group, generation of a guidance document on the conduct of clinical trials in pediatrics, and finally, the proposed pediatric rule.

[Slide.]

"The List" was generated in consultation with pediatric experts. It should be noted that approved drugs include both prescription and over-the-counter drugs approved under a new drug application.

The following criteria were used to develop "The List." The drug product, if approved for use in the pediatric population, would be a significant improvement compared to marketed products, or the drug is widely used in the pediatric population as measured by at least 50,000 prescription measurements per year, or the drug is in a class or for an indication for which additional therapeutic options are needed.

"The List" was published on May 20th, 1998, and will be updated periodically.

[Slide.]

A Guidance for Industry on qualifying for pediatric exclusivity has also been made available. Until regulations are issued through notice and comment rulemaking, this guidance has been made available to assist industry and FDA in the interpretation of the exclusivity

provisions of Section 111 of FDAMA.

[Slide.]

A Pediatric Formulations Working Group was established in 1995. Agency pediatricians, chemists, and other important contributors have been active in working on approaches to circumvent some of the chemistry and manufacturing barriers to new formulation development.

An FDA workshop on this topic was held in May of 1998. Communication between clinicians and chemists, government, industry, and academia was determined to be a significant outcome of this meeting. This group is also developing a guidance document that will address pharmacokinetic studies in the pediatric population.

[Slide.]

A clinical trials guidance document is being developed in conjunction with the American Academy of Pediatrics. This document will serve as the basis for Guidance to Industry on clinical trial designs for assessing safety and efficacy of drugs in the pediatric population.

[Slide.]

Finally, the proposed pediatric rule was published

August 1997 to ensure that new drugs and biologic products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments for children contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval.

This rule will apply to original applications of drugs classified as new chemical entities and includes antibiotics and new biologic products. Studies will be required to assess safety and effectiveness in pediatric patients only for the indications sought by the manufacturer.

Adequate pediatric data would be required to be submitted with the original NDA application unless FDA grants a deferral or waiver of the requirement.

A significant majority of the 54 comments received after publication of the proposed rule, received from pediatricians, professional societies and specialty groups, industry, parents, and patient groups favored the rule.

The proposed regulation is currently in the rulemaking process. The additional six months of

exclusivity granted to products complying the proposed requirement to obtain use and safety information, we hope will provide an incentive for sponsors to comply with the provisions of the pediatric rule.

In bringing these issues before you today, I feel very confident that I am, in a sense, preaching to the choir. This division and this advisory committee have recognized from the beginning of the AIDS epidemic the critical importance of the early development of drugs to treat HIV-infected infants and children, and to prevent neonatal transmission.

I believe also that sponsors have heard and responded to our message, as well, in most cases. However, as the future of antiviral drug development expands to the treatment of viral disease, such as hepatitis B and C, influenza, viral meningitis, and, who knows, the common cold, issues related to pediatric drug development may become more complex and, we hope, more frequent.

You may be asked to provide advice on these issues. The pediatric community believes the risks of not providing adequate use and safety information for important

medications are far greater than the potential risks associated with the scientifically sound study of these medications, and FDA agrees.

Thanks very much.

DR. HAMMER: Thank you.

DR. BIRNKRANT: Are there questions for Dr. Cvetkovich on the pediatric initiatives?

DR. HAMMER: Dr. Hamilton.

DR. HAMILTON: Would drugs that might be used in pregnant women be included in this category?

DR. CVETKOVICH: As far "The List" goes?

DR. HAMILTON: Yes.

DR. CVETKOVICH: No, pregnancy is not included.

DR. BIRNKRANT: Dr. Feinberg.

DR. FEINBERG: Of specific interest to this committee, are there drugs that we have reviewed or are going to review that are already on this list?

DR. CVETKOVICH: Each division received a list of all the drugs under their purview and determined whether there was a need for inclusion of the drug on the list, so there certainly are drugs in our division which are included

on the list. If you are interested, we can get you a copy of that.

DR. EL-SADR: How long is the list? How many drugs are on the list?

DR. CVETKOVICH: Well, it is complicated in that, in general, any drug with an indication that could be included, that the adult indication could apply to children, is in general included on the list, so as you can imagine, this is quite a long list.

DR. EL-SADR: I thought you also had to fulfill the criteria of 50,000 prescriptions or something.

DR. CVETKOVICH: The criteria are "or" instead of "and," so if the drug would provide significant benefit or the 50,000, so, yes, the list is quite comprehensive.

DR. MURPHY: There is only thing I wanted to make sure you understood, there is the list and then there is the priority list, and basically, the list is the Orange Book of approved drugs for which there would be an indication that children would need the therapy.

The priority list would be the one, I think, that we could send out to you.

DR. BIRNKRANT: Dr. Lipsky.

DR. LIPSKY: I am just curious where the six-month exclusivity extension came from. Was that some sort of economic calculation?

DR. CVETKOVICH: This was mandated by Congress as being perhaps a carrot to industry to conduct these studies, and I think that it remains to be seen whether this is going to be a wonderful carrot or how it will work exactly.

DR. LIPSKY: Is the feel that that is a tiny carrot or a big carrot?

DR. CVETKOVICH: No, I think it was determined to be reasonable.

DR. MURPHY: I think it is a big carrot, and let me tell you why. First of all, it is in Congress' wisdom, so we don't know all the calculations that went into that, but the reason we think it is a big carrot is it doesn't apply to just a specific formulation. It applies to the active moiety, so if they do a pediatric formulation or do a study in children, and they go through the process that has been outlined in the guidance, and have submitted a written request and they meet the requirements of the written

request, and they are granted exclusivity, it would be for the entire active moiety.

So, if they have a blockbuster adult component, and it has the exclusivity to be appended to it, then, they get six more months of exclusivity on that adult product.

DR. LIPSKY: I realize that if you have a blockbuster, that certainly would be a significant amount. The question is if you don't have a blockbuster, I would presume that industry will do a very cold economic analysis on what they expect, you know, what would be, roughly 10 percent more exclusive, whatever, is that going to be worth the money and the effort for, you know, pediatric clinical trials.

DR. MURPHY: I don't want to put this out as a fact, but I will tell you that I was impressed by the amount of money that is made per month by extension of some of these products, so I am sure it will be figured out, but it's impressive

DR. HAMILTON: Speaking of exclusivity, this is from a novice here, to what extent is it incumbent upon this committee to recommend to the manufacturers of drugs the

inclusion of groups that perhaps they haven't included in their original indication? Let's say you had a disease that was easily studied in adults, but the prevalence of the disease was a lot higher in children, and they presented an indication for adults. Can we, in effect, hold them hostage, do we want to, how does that work?

DR. MURPHY: We really can't hold them hostage, but one of the things that is provided by the process as presented here, is that we -- meaning the FDA -- can ask for them to submit data to a certain age group, if you will.

I think that any time that the committee makes a recommendation that an age group be evaluated, that the agency would take that very seriously to try to put that together as a request to the company.

DR. JOLSON: This kind of ties back with your previous question about Phase IV commitments, and probably based on the sort of guidance that we got from this committee when an application was presented, we would request that the sponsor make a voluntary Phase IV commitment for further development or dose finding in a particular patient population, whether it could be

pediatrics, it could be an elderly population, it could be patients with renal failure or liver failure, or any patient population that you think requires additional study, at that time would be an appropriate time to make that a Phase IV commitment at the time of approval.

DR. LIPSKY: I would just remind the committee that sometime ago, parents of children with AIDS made a pretty dramatic presentation in front of this committee, and this committee then voted later that day that the committee would ask for reasons -- I believe the vote was we would ask for reasons, if data were not presented to the committee about the use of a drug in children, why that wasn't, and what would be the mitigating circumstances.

I believe we voted on that.

DR. HAMMER: We had a consensus of the group. It wasn't an official vote for the record, but it was a strong consensus of the group the desire to have pediatric data presented at the time of accelerated approval applications that came in front of this committee or good reasons why not if such data were not available, you are correct.

DR. JOLSON: And I think that the Division has

clearly heard the message from this committee, and I think that industry is aware, as well, and you should know that throughout drug development, when we speak with sponsors, at every opportunity we do remind them of the need to develop a pediatric formulation or pediatric dosing information.

Occasionally, it is difficult because of the particular drug product, it may be difficult to have a satisfactory, well-tolerated formulation, but we clearly have heard the message from the committee, and part of that is because this committee has been so clear about the need to do that, and do that early. We thought you would be particularly interested to see that now regulation is kind of catching up with the spirit of what your advice has been.

DR. MURPHY: I want to say that I think that is really exactly what is happening here, and I think this committee has provided advice which has been listened to and has been acted upon, and if you look at antiviral drug development, there was a time in which we were very concerned why the committee made that statement, but I think it is definitely improving, and I think that your activism in this area has helped.

DR. BIRNKRANT: Other questions?

Thank you very much. It looks like we are ahead of schedule this morning, so why don't we plan to take a break at this point in time and reconvene about 9:45.

[Recess.]

DR. BIRNKRANT: We just wanted to clarify some of the issues that were raised in the first portion of this morning's meeting, related to pediatric initiatives and use of drugs in pregnancy.

With that, I will turn it over to Dr. Jolson and Dr. Murphy.

DR. JOLSON: Before we move on, it is probably just worth, as Debbie mentioned, just clarifying these two points. One has to do with the pediatric initiative and the issue of a list that was published in the Federal Register.

I can't really speak for other divisions, but for this particular division, essentially, all of the products that you would be familiar with, the antiviral products, would be on the list provided that there was an adult indication that we thought would be reasonably relevant to use in children and that there was a need for dosing

information in some pediatric age group.

So, for example, a drug that currently has pediatric information, but perhaps doesn't have dosing information from birth to age two, would have made that list. So, I just wanted to mention that, so that you would realize that really most of the products that you are familiar with from this division would have been on that list, and that there was no like higher selection process in terms of prioritizing them.

We will be happy to actually provide you with the list, but it is reasonably comprehensive if we thought that the drug could potentially be used in children, but needed more dosing information.

DR. HAMMER: Thank you.

DR. JOLSON: The second question that was raised, which is really relevant, and I just didn't want to leave it without just giving a brief mention about, in terms of what is the agency doing and thinking about in terms of use during pregnancy, and I think Dr. Hamilton may have raised that question.

It is really important. I don't want to just

leave the question without letting you know that there is a substantial amount of effort that is being devoted to making certain that the pregnancy section of drug labels is updated and provides more useful information.

Sandy Kweder, who is the Deputy Director for our office, I asked her to comment on this because she is the co-chair of the Pregnancy Labeling Task Force for the agency. So, I am putting her on the spot.

DR. KWEDER: That's okay. I could do this in my sleep.

The issue of pregnancy and actually labeling of drugs for use in pregnancy is one that is very important in the Center and the agency overall. There is, as Heidi mentioned, an initiative that we call the Pregnancy Labeling Task Force, that crosses all centers of the FDA, not just drug, although most of the activity has initially been focused on drugs.

It is separate from pediatrics, but I think it indeed is a natural extension of concerns about that patient population because of the numerous issues involved in the administration of drugs to neonates and when is a baby a

baby.

But just to give you a thumbnail sketch of some of the things that we are doing, and you will likely hear more about in the future, this task force was initiated because of persistent complaints, and probably appropriate badgering, from many professional groups about the current labeling system of pregnancy categories that you are all probably at least a little bit familiar with, the A, B, C, D, X.

I won't go into what those concerns were, but basically, we held a public hearing last fall and had extensive testimony, verbally and in writing, that leads us to believe that the current system needs to be revamped completely for a lot of different reasons.

Any of you who have had the experience of trying to decide whether or not to prescribe for a pregnant woman and try to use the current system, or the experience of having a woman who is already pregnant and has been taking a drug, and she is trying to decide what to do about that pregnancy, has experienced an anguish of this doesn't help me.

So, we are in the process -- and it is a very difficult process -- of trying to rethink how to do that. The reason that I mention that is that has been our primary focus, but the task force doesn't see that as the only issue surrounding pregnancy labeling. The real problem is lack of data, and we hope that wherever we come out with labeling along the way, we will raise the standard for data collection, and I think some obvious areas that this committee has dealt with in the past, particularly with antiretroviral drugs, is pharmacokinetics in pregnancy and dosing. Pregnant women do have illnesses, and they do require drug treatment, and we think that it is appropriate where women need to be treated when they are pregnant to study the pharmacokinetics, so that the next patient who needs that medication, that her physician has better dosing information.

We are also in the process of developing a guidance document for the industry on some considerations for when and how to conduct pregnancy registry studies, usually in the post-marketing phase. Some of that has been done, as you know, with acyclovir in the past. There is the

antiviral pregnancy registry that is ongoing on, and a registry is not a registry is not a registry. There are many ways to do that, and we will be trying to provide some guidance to the industry on what we think is important in that area.

So, those are just a few of the things that we are doing. You will hear more about that in the future, and I wanted you to know that we think this is extremely important, and a lot of the work that has been done in the Antivirals Division really has begun to set a standard for the rest of the Center that has not had to deal with this in much detail.

I can answer any questions now or at the break.

DR. BIRNKRANT: Thank you very much.

Well, this morning we have heard about agencywide initiatives that impact our job at the FDA, and at this point in time, we will hear about initiatives that more directly affect the Division of Antiviral Drug Products and their work on a day-to-day basis.

Our first speaker is Dr. Jeff Murray, who will provide an overview of regulatory procedures as they relate

to accelerated and traditional approval, and as I mentioned, as a follow up to our meeting a year ago on this topic.

Accelerated and Traditional Approval Mechanisms

DR. MURRAY: Good morning.

[Slide.]

Topics of a regulatory nature that I will be addressing are accelerated and traditional approval, touching on post-marketing commitments, the use of HIV RNA as an endpoint for drug approvals, and current recommendations for trials assessing a new dosing schedule.

[Slide.]

First, I would like to review just some of the accelerated approval regulations by quoting some passages from the CFR, if you will.

[Slide.]

First, accelerated approval regulations state that the regulations apply to drugs that, first, "treat serious or life-threatening illnesses and provide meaningful therapeutic benefit to patients over existing treatments." Then, the regulations actually list some examples, and examples which should be by no means intended to be

inclusive, but an "ability to treat patients unresponsive to or intolerant of available therapy, or drugs that have improved patient response over available therapy."

[Slide.]

Now, with accelerated approval in clinical trials, you can use endpoints other than irreversible morbidity or death, and that is good, you can use surrogate markers, but in the past when you have done this, and shown your activity with a surrogate marker, an accelerated approval has been subject to the requirement that the applicant study the drug further -- and this where your post-marketing commitments come into play -- and to verify and describe its clinical benefit, and I think this is kind of key because this is how we are interpreting it, where there is uncertainty as to the relation of the surrogate endpoint to the clinical benefit, so to study it further when there is uncertainty for this relationship.

[Slide.]

When you study it further, when the applicant is studying the drug further, there are several types of post-marketing commitments, actually two: accelerated approval

and Phase IV commitments, so just kind of comparing these two.

The accelerated approval commitments are required. These studies are required, they are binding with the agency and the sponsor in contrast to Phase IV commitments, which are a written agreement from the sponsor, and they are done under good faith.

Got accelerated approval commitments, it is confirmation of the efficacy, so where there was some uncertainty in your endpoint from your study supporting accelerated approval, you are supposed to confirm that efficacy with your studies for traditional approval.

Usually, these studies were already or supposed to be already underway by the time the NDA for accelerated approval has been submitted. One of the reasons why the accelerated approval commitments are binding is because there is an expedited withdrawal process of the drug for failing to meet these commitments, and there is no such procedure for the Phase IV commitments.

Also, as far as the Phase IV commitments differ in the type of studies as Dr. Jolson had mentioned, that are

done, whereas, accelerated approval, its confirmation of efficacy in Phase IV commitments, it is to study unresolved issues that might come up at the advisory committee like, you know, drug interactions, mechanisms possibly for adverse events, and studying various patient subgroups, patients might have liver failure, renal failure.

[Slide.]

So, exactly a year ago, on July 14th and 15th of last year, we had an advisory committee, and since then we have had a slightly different approach for accelerated and traditional approval based on that meeting.

[Slide.]

The title of that session one year ago was "Use of HIV RNA as an Endpoint in Clinical Trials." The conclusions that we gathered from that meeting--and I believe that we had the consensus of the committee on this--is that, first of all, HIV RNA, measures of viral load, plasma HIV RNA, is a suitable endpoint for both accelerated and traditional approval, and that clinical endpoint studies should remain an option and maybe preferred under certain situations possibly, and that CD4 changes and clinical endpoints should

be collected in all studies and should be consistent with the HIV RNA changes.

Now, there are precedents for lab endpoints. We approve drugs to lower cholesterol based on following cholesterol and use glucose as an endpoint for looking at antihyperglycemics. So, this is certainly nothing new.

[Slide.]

So, last year, on July 14th, we devoted a day to showing the relationship between HIV RNA changes and clinical benefit, and that was to convince ourself that there was a little uncertainty between treatment-induced changes in HIV RNA and clinical benefit, and where there is a little uncertainty, then, this could reliably be used as an endpoint as for other drugs, cholesterol-lowering agents, for example.

How we did this is that there were many people participating in this, different sponsors and different groups participating this meeting, and we showed five different analyses, some of them pooled studies, and overall, in column 2, the number of patients overall for the five analyses amounted to about over 5,000 patients

receiving different regimens, some of them protease inhibitor regimens, some of them dual nucleoside regimens perhaps not the way they are used today, but I think this even makes a stronger argument that perhaps even in less than optimal use, we are able to see this relationship, and then across a range of CD4 counts, ranging from like a median of CD4 counts from this study from 21 to over 200.

[Slide.]

In all of these analyses, we saw that greater reductions in HIV RNA were associated with lower risks of disease progression, and it was striking that this was shown in a dose-response type manner.

We also saw from one analysis, I think one by Pharmacia & Upjohn, that more sustained reductions in HIV RNA were associated with lower risks of disease progression, and we were quite happy that these conclusions are consistent with biologic theory and current treatment guidelines, and that, in theory, you know, if you can reduce your HIV replication to practically nothing, you will have little or no mutations developing, and the consequence of that is less or no resistance and a more durable response,

and in the end, if you have a more durable response, hopefully, greater clinical benefit.

So, I guess the question that we really weren't able to answer exactly would be how much RNA reduction and for how long, and I think at the end of the meeting, that there was somewhat of a consensus that if you could follow patients for at least 48 weeks or about a year, and you have a durable HIV RNA suppression below the limit of quantification when possible, that that would with reasonable certainty confer some clinical benefit.

In a lot of these analyses, it was even shown that lesser degrees of RNA reduction, perhaps around a half a log, around actually the variability of the assay measurements themselves actually could confer some clinical benefit, but to reduce the uncertainty, we wanted to make sure that we had a rigorous endpoint and a high enough hurdle, so I think for traditional approval, what we have now been telling sponsors is at least 48 weeks of a durable HIV RNA benefit, and I think in this way we are going to be safe and that likely to predict some clinical benefit.

[Slide.]

Just to compare and contrast the old and new paradigm for traditional approval is that the old paradigm was that clinical endpoint studies were required, it was the only way to get the traditional approval, and they were based, the clinical endpoints were the development of AIDS-defining events and/or death, and AIDS-defining events could include anywhere from 20 to 25 or more endpoints consisting of opportunistic infections, and those were being added and subtracted from protocols as deemed appropriate at times, they weren't always exactly the same.

New paradigm is that clinical endpoints, of course, are still an option, but also there is another option and that is to show durable HIV RNA suppression, durable, our definition at this time meaning at least 48 weeks of followup in the last patient enrolled in the trial.

We did kind of put out a proposed primary endpoint at the last meeting, and we thought that a time to loss of virologic response would be an endpoint that would be really workable, doable in clinical trials, but we would also look at the proportion below limit of quantification or limit of detection or whatever it is at the time, and wanted to also

make sure that CD4 changes in clinical endpoints, as they were collected in the studies, would be consistent with what we are seeing going on with HIV RNA.

[Slide.]

So, what exactly is loss of virologic response besides it being our primary endpoint? Well, I think this can differ depending on the population. For a naive population or population who haven't experienced the drugs of interest, I think there has been enough data presented in the last year, on July 15th, as well, to show that a large majority of patients can suppress with a combination of treatment their plasma HIV RNA to below limits of quantification.

So, we thought that this was probably a good hurdle for that population, however, we also realized that other definitions may be appropriate for other populations, maybe in patients who have had all the available marketed regimens and are likely to be drug resistant, there might be other populations, as well, that achieving levels below the limit of quantification might be too high of a hurdle, so in that case, loss of virologic response will have to be

defined, virologic response and loss of virologic response will have to be defined, and we will accept reasonable proposals for that depending on the population.

So, what is loss of virologic response? Well, we view it as a rigorous study endpoint, and what it is not is it is not necessarily the same as clinical or immunologic failure, meaning that although somebody has achieved this study endpoint, they might still be deriving benefit of the drug, not meaning to say that complete viral suppression means you have totally lost benefit from that drug.

So, it is also not necessarily the same as patient management criteria in a protocol. Physicians, a patient may choose to stay on a drug even after they have achieved the rigorous study endpoint. The rigorous study endpoint is to make sure that we were certain that we had a relationship with eventual clinical benefit.

[Slide.]

Now, before we have the HIV RNA option for traditional approval, as you are aware, clinical trials are becoming quite difficult to conduct and sometimes enroll, and with the onset of more and more potent combination

treatments, realized that there is a lower and lower number of endpoints--and I think we have seen this all across the country, that the frequency of opportunistic infections have been going down--making it very hard to conduct long-term clinical trials especially in the setting of routine monitoring of HIV RNA and frequent treatment switches.

So, I think that last year we all realized that HIV RNA endpoint could surely be practical and could solve many of the clinical trial problems, dilemmas, that we were facing.

Here is kind of a graphical example of how the time to virologic failure endpoint works and some of the advantages. At week zero in this hypothetical patient, you have somebody starting with a baseline log HIV RNA, plasma HIV RNA, of 5.2 or thereabouts, starts treatment, HIV RNA drops actually to below the lower limit of quantification. For this example, we are using 2.6 logs, that would be 400 copy number for Roche Amplicor, and then at about week 28, the person is still below the limit of quantification, but then comes above at week 32.

So, at week 32, once a measurement above the limit

of quantification is identified, a second one is obtained to make sure that this is not lab variability, just to confirm that actually there has been a rise in viral load, and at this point, that is when the endpoint has reached, and the beauty of this is that the endpoint is captured before treatment switches.

I think this has a high degree of patient acceptability, what I call statistician acceptability, tends to reduce confusing missing data. Also, it coincides with clinical management, that is really nice, and another advantage of HIV RNA is that it does provide economy of sample size. We are able to do trials of a more reasonable size than we would have if we had to use only clinical endpoints in the setting of potent combination treatment.

[Slide.]

One of the goals in kind of accepting a new paradigm would be to make sure that an accelerated approval process could be preserved, because we realize that there still exists a need for more treatment options. Even though we have good drugs, some people are burning through them pretty fast.

Even though we are using HIV RNA endpoint, and it is a pretty dynamic, rapid way of evaluating drug activity, two, 48-week trials still might not be fast enough for some promising drugs, so there still is an option for accelerated approval based on shorter term HIV RNA data.

Shorter term HIV RNA data in combination regimens, you have to realize that it is not always to discern and isolate the effect of one drug in a combination over a short period of time, so with shorter term data, there will be a little bit more uncertainty with endpoint than longer term data. So, that is why the shorter term data with HIV RNA endpoint is under accelerated approval, and the longer term data is considered confirmatory.

Now, sponsors are encouraged to study populations in need, and when a drug gets approval, accelerated approval, it would be nice to have information on how these drugs work in the populations who need them the most. However, we realize that it is also sometimes difficult to do a clinical trial in populations who have exhausted all other regimens, because it makes it very difficult then to pick an adequate control arm, so what is your control arm.

So, we realized that the sponsor may not necessarily be required to prove that a drug fulfills a special niche within a specific clinical trial, that there might be other information on the NDA package that would help to decide that, like a convenient dosing regimen, its overall safety profile. There are other considerations. You have just been studying, you know, patients who have failed or intolerant or resistant to all drugs, because that clinical trial is not always easy to do.

[Slide.]

So, for accelerated approval, also using HIV RNA as a primary endpoint, haven't abandoned CD4, it is still very important, CD4 changes should be consistent, however, we felt that it was easier to power a study based on one clinical endpoint for doing your sample size calculations, and it is easier to have one endpoint as primary.

The old method that we were using, usually, we were comparing mean changes from baseline over time, used a metric called DAVG, which was average changes over time, however, due to the limitations of the assay, we found out that mean changes were not that discerning, everybody was

kind of hitting the floor, so a new method that we have been looking at is comparing proportion below a limit of quantification at, let's say, like 24 weeks, and again realizing that for some populations, proportion below LOQ may not be feasible.

Then, the duration of data for accelerated approval, sponsors have generally have submitting NDA packages when they have crossed the 16-week mark, but by the time the NDA or the drug of interest goes to the advisory committee, or before approval, we would like 24 weeks of data to look at, especially drugs, you know, studying triple, quadruple combination regimens.

[Slide.]

The last topic, and it is kind of sort of related to our new paradigm for accelerating traditional approval, and that would be evaluation of new dosing schedules, let' say going from a TID regimen to a BID regimen, or a BID regimen to a QD regimen, and we realize the importance for patient adherence and for actually perhaps, you know, long-term antiviral effect, we realize the importance of getting a compact, easy-to-take dosing regimens.

So, we would like to make it a simple process to go from one new dosing schedule to another, but when you look at it, you realize that there are difficulties, in fact, it is difficult to make an argument based on PK alone because we really don't have very much information on pharmacokinetics and how they affect viral load for most of the drugs, I don't really think for any of the drugs, so it is difficult to make a PK argument, and when you are going from a TID to a BID dosing regimen, you can probably be pretty sure that Cmax, AUC, and trough, they are not going to be the same, they are going to differ.

So, we decided that probably the best way would be to show similarity in activity, and in that we now evaluate drugs in the setting of combination therapy, showing marginal differences between dosing schedules might be difficult over a short period of time, and so we would like commitment from sponsors to have 48 weeks of followup on changes in dosing schedule type studies, as well, and that we can make decisions based on 24 weeks if the data is really compelling and, of course, we think there is a real need and that it would offer therapeutic advantage to go to

the new dosing schedule.

[Slide.]

An example that we have used as a rationale for 48-week studies is Agouron Study 511 in which nelfinavir 750 mg three times a day versus a lower dose of nelfinavir 500 mg three times a day was studied in combination with AZT and 3TC.

At 16 weeks there was significant differences between those two different doses. Now, these are two different daily doses. You have got to remember in new dosing schedules we would generally be giving the same daily dose, but just at different times a day, so the differences could even be smaller for those comparisons, but for two different doses in combination therapy--because all the drugs are pretty potent--no differences at 16 weeks except for a subgroup. The subgroup was people starting with baseline HIV RNA greater than 100,000.

However, at 40 weeks, there was a difference that was I think pretty clearly recognized for the proportion of patients who were below the limit of quantification, and the difference was about 18 percent. It was a difference of 86

percent versus 68 percent.

[Slide.]

Here, you have the three treatment arms, the top one being the 750 mg dose of nelfinavir and the one that looks the same. You really do start to see an diversion or a separation of the curves at 16 weeks, but at that time not yet clinically significant, I mean statistically significant, didn't really start getting statistically significant until after 24 week and pretty clearly evident at 40 weeks.

So, based on what we know about combination therapy and the activity of drugs, we think we might be able to make some decisions early if the data looks really good, but we would like a commitment for longer term followup to be submitted to us just to make sure that in the long run we are not making a mistake and we are not kind of sliding slowly, sliding back on the gains in drug potency that we have made in the last several years.

With that, I will conclude my remarks, if there are any questions.

DR. BIRNKRANT: Dr. Feinberg.

DR. FEINBERG: Jeff, what you have outlined in terms of the standard for efficacy, you know, your whole presentation has been in the context of HIV disease, but what about some of the other antiviral indications that we are looking at like hepatitis, for example, and where people are also quantitating viral load?

DR. MURRAY: I wish I could comment more on that. It would be nice if we could bring up to speed other viral illnesses and perhaps someday we can use some of the same models that we have used for HIV to help the progress with the study of other viral illnesses.

Right now the assays for a lot of the other viral illnesses may be hepatitis C or not, probably is as good as the HIV RNA assays, and there is not as much clinical trial evidence supporting a relationship between those changes and clinical benefit, but it seems likely that for some of them, these correlations will be identified and this paradigm might fit for them, but right now we are reserving this kind of paradigm for the antiretroviral drugs.

DR. FEINBERG: So, in essence, what you are saying is that that is a desirable goal if the parallel data are

presented that the reduction in viral load, say, for hepatitis B correlates with clinical -- you know, long-term clinical benefit, then, we would move this paradigm into the evaluation of the other diseases.

DR. MURRAY: Yes, it would probably make a very interesting advisory committee in the future for you all to give us some consensus on that issue.

DR. BIRNKRANT: Dr. Hammer.

DR. HAMMER: Let me back up a little bit to the early phase of development and some of the early data that one might look at, and we might see in presentation, and that is, what is the agency's position on trying to tease out the activity of single new agents as they come, both agents or current classes and particularly agents of new classes, for example, integrase inhibitors when they come before us, as far as the periods of monotherapy that are going into trials, whether they be 7 days, 14 days, 21 days, as opposed to being up-front tested in combination regimens? Is there a requirement to see individual activity-- obviously, it is preferable to see individual activity--but what is the agency's position on this or is this a position?

DR. MURRAY: You are asking about earlier Phase I-II monotherapy trials?

DR. HAMMER: Yes.

DR. MURRAY: I don't know that we have an official position on this. There are clinical trials where monotherapy is being studied early on for a brief period of time, for two to three weeks. There is some evidence to suggest that if you do it for that limited period of time, that you don't jeopardize individual patients probably.

Of course, we don't have the absolute longest term followup on those, but it looks like that it is probably pretty safe to study drugs for two weeks without jeopardizing patients to drug resistance too much, however, this is a topic, I think, of interest. We have actually been discussing this with the Division of AIDS, and realized that there is a lot of anxiety about studying monotherapy for any period of time. In fact, does a period of monotherapy give you information that is evaluable in any way? We think it does, but do we know that for certain?

That could be a topic of discussion in future, perhaps in workshop and a future advisory committee, but we

haven't come to any firm conclusions, and we would certainly like input on that.

DR. HAMMER: Thank you. One quick question about the time to virologic failure endpoint, a statistical quality question I guess. Obviously, the time to failure is easy to calculate when someone goes below the limit of quantification and the rebounds. In someone who never responds, in your view, is that an immediate failure, or is there some arbitrary point that is chosen statistically when that person has failed?

DR. MURRAY: Well, it has to be well defined in the protocol, and, you know, if a person is not going below limit of quantification, you know, you have to allow a sufficient amount of time for this to happen, but the treatment guidelines have stated, at least the DHHS Kaiser Family Foundation treatment guidelines state that if you are not reducing a log, HIV RNA, in about four to eight weeks, then, you might want to consider a treatment switch, so a lot of protocols have incorporated that into their design, and if they are switching at that point, then, those individuals will be classified as a treatment failure.

We realize that it is somewhat arbitrary. The important thing is, especially in, if open label, is that we have very consistent, well-defined protocol designs where the same thing is happening to all individual participants in the study.

DR. HAMMER: Thank you.

DR. BIRNKRANT: Dr. Bertino, then, Dr. Pomerantz.

DR. BERTINO: On your last three slides, you kind of touched on about new dosing schedules and kinetics. I understand the pressure, political pressure and pressure from the medical community and patient community to get these agents out on the market.

It seems, though, that we are kind of ignoring tailor-made regimens for patients and looking at kinetics and dynamics incorporating them into these treatment regimens, and with the goal of optimizing therapy, reducing toxicity, and preventing viral resistance specifically for HIV.

It's a complex study, but, for example, we don't understand what happens to the pharmacokinetics of protease inhibitors when you have a patient that starts out with a

high viral load, you knock it down, do their kinetics change of whatever, because reduction in viral load, et cetera.

So, my question really is are you thinking about incorporating these kind of things and using kinetic, dynamic data in vitro, dynamic data from hollow fiber models, et cetera, into the design of these accelerated approval trials?

DR. MURRAY: We really haven't addressed that specifically, and I agree with you, it would be very nice to be able to monitor and tailor-make your regimen for patients based on the levels that they are achieving because we do know there is quite a bit of intersubject variability for most of these drugs and there is changes that are occurring as they are getting treated.

We would be very interested into looking to those relationships. At this point I guess we just don't have enough data and information to propose some guidance or some, you know, our current thinking on that manner, but that can certainly be topics for future discussion, perhaps as workshops or further advisory committees.

DR. BIRNKRANT: Dr. Pomerantz.

DR. POMERANTZ: A statement and a question. I think that slide is good to stay up there because it says percent less than 1,200 RNA copies per ml, and I think that sort of illustrates how there is a spectrum in how the field looks at what limit of detection of success really is. With one group--and I hope I am not overstating it--but my friend Bob Coombs has written in the ID literature that we should not forget that RNA is just a marker and that there are a number of clinical endpoints, and then you have the group like Doug Richmond and others of which I actually am a member, I feel, who want it less than 50, less than 50, better than less than 400 for sustained, and David Ho has even gone so far as to say latency is really just small areas of viral replication that are continuing to happen.

So, that being said, it is very clear I think in certain patients that you want to get it as low as possible, ablated to the limit of quantitation that you are able to achieve, but there are in the real world, as you pointed out, I think nicely, a group of patients that are not small, that have gotten many different drug combinations, and are now involved with, to use an oncological phrase, salvage,

and I have been impressed by the fact that in the literature, there has been defined a group of patients that get very little viral response RNA or it comes back to near baseline after some initial period of some suppression, and yet those people seem to be doing better than those that were not treated both immunologically, both CD4 counts, activation parameters on their CD4s and CD8s, so there is this question of whether there is a change in the pathogenesis of those viruses, that you now have a best-fit virus for this environment, but that the viruses, the quasi-species, are less pathogenic.

How are you going to dissect out those groups, because they are going to become more and more important as more and more people in the country get treated, how are you going to dissect out the groups that don't get a big RNA response, but are having an immune response possible through the hypothetical change in best-fit pathogenesis model virus?

DR. MURRAY: I guess I can say this is all work in progress, you have to remember that so far we haven't gotten an application under this new paradigm, so, you know, we

will probably have to plod along through some of this, and I don't really have the answer to your question other than to say that, you know, we are not dogmatic about achieving limit of quantification for everybody, and we realize the need to perhaps look at a combination of endpoints, look at other endpoints, look at CD4 with HIV RNA changes, and, you know, for special population groups, the data will have to be presented and we will have to make our best decision based on the scientific data at the time, so I guess it's work in progress.

DR. POMERANTZ: I agree.

DR. MURRAY: Do you have any ideas on that, Roger

DR. POMERANTZ: Yes, that is reasonable. I think that you can say up-front that for naive patients and patients who haven't been really treated very aggressively, you want to ablate viral replication, you want to get it down below 50 if you can, and you want to look at what percentage of people that can happen.

But when you start looking at the other ones, I think you have to look carefully at immune parameters, maybe substitutes, or even clinical endpoints, because you don't

want to turn back the clock, but there are a lot of people that need salvage, that maybe we are able to affect the viral qualitatively, if not quantitatively.

In those groups of patients, I would, as you were saying, just keep your eye on not always saying what I think is probably the best thing we can achieve, which is viral ablation to the limit of detection, but you have to look in those people back at some of the immune parameters, and you may even have to factor back some clinical endpoints.

DR. MURRAY: I think that is entirely correct, yes.

DR. BIRNKRANT: Dr. Masur.

DR. MASUR: Jeff, could you expand a little bit on what drug absorption and drug interaction studies you would require at the two levels of accelerated approval and final approval?

DR. MURRAY: You mean would drug interaction studies fall under--some fall under accelerated approval and some fall under Phase IV commitments?

DR. MASUR: Well, for instance, under accelerated approval, one of the problems is if one provided this

package, it is very difficult for a clinician to know how to use it when one is using it in combination with a variety of other drugs, so there are safety issues obviously.

Do you have some paradigm for what kind of studies you would require as the minimum cut to fast track, one of these drugs for accelerated approval?

DR. MURRAY: I don't think we have set minimum standards in the form of a document saying that you must do, you know, your choice of three out of the four following drugs. I think we have generally taken it on a case-by-case basis, and it really depends on how the drug is metabolized and excreted.

Certainly, for P4503a inhibitors now, there is laundry lists of drugs that need to be studied. Of course, if the drug is going to be used in combination, if it is an NNRTI, it is going to be used in combination for protease inhibitor, we would like PK data on as many protease inhibitor NNRTI combinations as can be done. I don't think we set a minimum standard. I don't know if you want to comment on that, Dr. Jolson.

DR. JOLSON: Whether it is accelerated approval or

traditional approval, the sponsor would still have the same obligation to provide adequate information on the label for the product to be used safely, and really the only thing that distinguishes the traditional approval from the accelerated approval is time. Right now it would be duration of followup in surrogate marker studies.

But in terms of the other requirements for an adequate safety database, and whatever drug interaction information or pharmacokinetic information is necessary to prescribe the drug safely would be required at the time of the initial approval, which would be accelerated approval.

DR. MURRAY: A lot of these we are trying to get done before the accelerated approval. Of course, if your study is in combination, if your NNRTI is in combination with a protease inhibitor, you had better have the PK data.

DR. BIRNKRANT: Dr. Feinberg.

DR. FEINBERG: Jeff, I want to follow up on two other comments. Actually, when Scott talked about how to look at these drugs for activity in an earlier phase, I actually have also a concern about how we are going to define viral load activity in Phase III, because there are

studies being designed where the new drug is added as a single new agent to patients who have essentially met the definition of virologic failure, which is that they have measurable viral loads, usually above 5- or 10,000.

Even though the single new agent versus placebo was usually for a limited time period, like four or eight weeks, it still I think raises a lot of questions about the appropriateness of that design.

You can see why it would be statistically favorable because you get up to placebo control for that limited period, and so the n's are smaller and you generate the data faster, but I guess what I am asking you is that a reasonable or acceptable design for Phase III.

DR. MURRAY: Well, adding onto your best current therapy or your current therapy at the time, it used to be kind of a convenient design, and I realize that it might not necessarily be the best way to dose patients because basically you are giving them sequential monotherapy.

I think probably the better design that we would try to encourage would be adding your drug X plus two new, let's say, NRTI's, or if you didn't have any NRTI's, maybe

recycled ones, so adding two drugs with your drug plus the same two drugs plus another drug that is already approved, that would probably be the preferable design rather than just adding one at a time, is to make comparable changes in the other drugs across both arms, trying to keep those regimens as constant or nearly constant as possible, realizing that that is difficult to do in the real world.

DR. FEINBERG: I guess I would say that I share your anxiety about the appropriateness of that placebo-controlled design as a Phase III, because I think it is somewhat different if it's a limited period of time as a Phase I.

To follow up on Roger's comment about other ways of measuring benefit, the common clinical experience that everybody has, of course, is that our hospitals are empty, and yet, you know, in real life practice, nobody has a clinic population where 80 or 85 percent of them are now below the limit of quantitation.

So, there is clearly something, and we may be not be measuring the right thing, but there is clearly something that confers clinical benefit because people aren't sick.

There is sort of a missing piece there, and that may be most important in patients who present in advance disease or with the highest viral loads since those are the people who you have a difficult time controlling just by looking at pure virologic criteria, and I think it would be very important, since this is a significant proportion of patients in the real world, that, you know, other ways of evaluating them beyond viral load reduction would be key, and I think may be a very important part of a sponsor's package.

DR. MURRAY: Right. Again, I think the limit of quantification was used as a high hurdle, and I think in some of the Glaxo-Wellcome studies presented last year, that they did find really very few individuals experiencing new OIs when the viral load was kept below 5,000. In general, you didn't have that many new OIs just even, you know, with lower levels of virus that you don't necessarily have to shut it off completely.

I think shutting off the virus completely is good for responsible use of your drugs and trying to prevent resistance, and trying to get durable response, but as everybody has stated, it is not always possible.

DR. POMERANTZ: Just as a followup, I agree obviously, I agree with Judy's point. We may be doing at times, even though I am a person that always pushes people in the clinics to try to ablate viral load in patients, we may be doing some patients a disservice, because many times you can get it down to 3,000, 5,000, and you are asked should you leave it there or should you go on to more experimental drugs, should you use hydroxyurea, and this comes up a lot, so I don't think it is a moot point, it happens routinely that if you hold to ablation, you can be pushed to great degrees, and maybe we shouldn't be, and I don't know that, but I think that your group is some of the ones that can bring the different studies together to try to get an answer to that.

DR. MURRAY: Right, and that is an interesting example, hydroxyurea, which can maybe help lower HIV RNA when used with maybe ddI and d4T, but also looks like it could have adverse consequences on your CD4 count, and I said before we want to make sure those changes are consistent, so that is something that would be, if we had a drug presented to the advisory committee, it would certainly

be a hard decision to make.

DR. POMERANTZ: That is a clear pyrrhic victory to ablate viral replication when you also ablate the CD4 count, and that is precisely what has happened with patients both in our center and around the country.

DR. BIRNKRANT: Dr. Lipsky.

DR. LIPSKY: In reference to the concern about drug interactions, do you see a role for in vitro testing of human P450, et cetera? Does that have any interest?

DR. MURRAY: I am probably not the best person to answer that. I don't know if we have biopharm people here. But I think there is a lot of agency interest on doing as much preclinical screening and trying to gather as much in vitro data as possible, because I think they do guide towards, you know, actually what human clinical studies need to be done as far as drug interactions, but try to move in that direction. Again, I am not the person probably to answer that question.

I might say that if you come to an advisory committee and there is an application presented where you are still looking at some mean changes or you are still

looking at a design that doesn't quit fit this paradigm, please be aware that a lot of trials have started a long time ago, some of the trials that might come forward started before last year's advisory committee, so we are still in a transitional period, and we certainly haven't reached that perfection point, probably never will.

DR. HAMMER: Dr. El-Sadr.

DR. EL-SADR: Thanks for the excellent presentation. I guess at each of these advisory committee meetings I always feel a little bit uncomfortable because we start talking about one year followup as long-term studies, it seems ironic, and 48 weeks is long-term followup, and often we provide accelerated approval based on six months or 24 weeks, and then what happens is these drugs are really used in a very different population from the population in which they were studied.

The median CD4s that you showed, I think the highest was 250.

DR. MURRAY: Yes, it was about 200 and some, right.

DR. EL-SADR: My struggle is--and I think a lot of

clinicians' struggle is--what does it mean six months separation of virus in terms of a patient who has much higher CD4, who is much healthier, and who is going to need to be on these drugs for eight, seven, 10 years.

So, I am a bit concerned about how we--I truly applaud trying to get more drugs out there rapidly, but I am very concerned that we are providing an incentive to study them in a very specific population, in fairly naive patients, fairly advanced or moderately advanced patients, and also, often with a comparative arm that is inferior to the study arm. There is a disincentive to looking really at drug-drug parallel comparisons, which is what is needed out there in clinical practice.

I am not sure what the answer is, but I am thinking that there may be ways of looking more seriously at including in your formula there, accelerated approval or full approval, the side effect profile, as well as maybe resistance. Certainly, people are going to stay on these medications maybe for a long time, and maybe we should look at the potential for development of resistance although, of course, we will see that more the longer we follow the

patients, so I don't have the answer, but I feel uncomfortable in extrapolating from six-month studies to longer term outcomes in our patients that we see in the clinic.

So, I think that was a comment rather than a question, but it is something that I think we struggle with in the committee.

DR. MURRAY: One thing I didn't say is that I think our safety database will be the same as we have been having in the past. I know it will be for accelerated approval, I didn't put it up there, but ICIH guidelines recommend for approval of a non-life-threatening drug, a database around anywhere from 3- to 600 for six months, non-life-threatening drug to treat for chronic use.

We have had around 5- or 600 most applications, and that is what we are still requiring for accelerated approval, so safety database is the same, and I think with two, a lot of sponsors are doing two to four or five trials sometimes, studying their drugs in different combinations, trying to show the various uses.

I think that we will be getting safety databases

that are about of the same size that were used in the clinical trials for drugs, I think some of the nucleosides that have been approved in the past.

DR. EL-SADR: When you look at the time to first failure, essentially, could you be losing important information as to what happens afterward? I think part of my decision in picking a drug is not only what happens with this drug, but what am I going to do with that patient further one, and many of these patients, once they fail on the study, they go on to some other treatment, and it might be just as critical to see their response to second choice.

DR. MURRAY: That is correct.

DR. EL-SADR: I think if we tried to get the sponsors to look more at their virologic endpoints, not clinical endpoints, but looking just beyond that first event, which is I think very clinically relevant to the patient and the clinician.

DR. MURRAY: That is true, and we do encourage followup on all patients, and I think that will probably be an excellent scenario in which to evaluate resistance once we kind of get sorted out what some of these assays can do

technically.

DR. EL-SADR: I had a question, I mean one issue, which is the dosing issue, because are you looking at--I mean I have seen studies presented where there are like 50 patients on TID and 50 on BID, and 16 weeks or 24 weeks Kaplan-Meier curve--are you looking for statistical equivalence in those studies or are you looking that things sort of look the same, because I don't know how to interpret that.

DR. MURRAY: Either approach, equivalence approach or a superiority approach, realizing that it might be harder to show equivalence over the short term. You want to be able to assess equivalence when there is an actual chance of detecting a difference.

If you are looking too early, at eight weeks, everything is probably going to look equivalent, so we know that is probably not a good time point, so equivalence trials are acceptable, superiority trials are acceptable. It becomes kind of sticky point about how long and how many patients to call it equivalent.

DR. EL-SADR: So, you are asking them for a sample

size that would demonstrate equivalence.

DR. MURRAY: Right. Our recommendations have been to power up your study, to using a delta of anywhere from 10 better to 12 percent, to power your studies for that, and we think that that will probably give us data that we will be able to interpret when the study is done.

DR. EL-SADR: My last comment is I still don't understand what you meant by sponsors encouraged to study populations in need, but what did you mean by that?

DR. MURRAY: We certainly encourage trials in patients who are advanced, have little treatment options, have failed or are deemed to be resistant, however, if we have a drug come forward that has only perhaps studied in naive or limited, you know, prior drug experience, but it looks like it has really good activity, and it's a convenient dosing regimen, and there is a little safety concerns, then, we think that that would, by the fact that it had the other advantages, would fit the spirit of accelerated approval, meaning that it had a meaningful therapeutic benefit over other drugs.

Necessarily, you wouldn't have to show that, oh,

yes, we showed this drug was useful in patients who had failed and were intolerant to everything, you don't necessarily have to do that trial. You can make your case for fulfilling the accelerated approval spirit based on other evidence in your package.

DR. BIRNKRANT: Other questions on this topic?

DR. MURPHY: Let me see if I can synthesize what I think I am hearing from the committee, is that with many of the new regulatory approaches, we seem to be addressing and meeting the need for access, and what I think we are hearing is a question about the balance as far as when we go into the requirements for the traditional approval or the followup, that you are concerned about addressing the adequacy of the followup, making sure some of these other questions are answered.

Is that sort of what I am hearing?

DR. HAMMER: I think that there is certainly a consensus among this committee that longer term followup beyond the specific endpoint of these studies that demonstrate benefit for the traditional approval based on an RNA endpoint would be certainly preferable and sponsors

should be encouraged to do that.

I also think that many of the points that were brought up in this discussion about longer term followup, resistance, pathogenetic underpinnings for what we are doing are the province of clinical trials groups working with pharmaceutical sponsors and that no single pharmaceutical sponsor with a drug is going to be able to answer some of these questions. It is going to be ongoing cooperative efforts to see what the longer term outcome over the next five or 10 years is going to be with what we are doing, which may be a good lead-in to the next topic.

DR. MURPHY: Thanks.

DR. BIRNKRANT: That is a very good point. Actually, as we approve and review these products in an expedited fashion, the post-marketing surveillance of the adverse events seen with these drug products are extremely important for the Division.

Our next speaker is Dr. Toni Piazza-Hepp, who will address how we are dealing with post-marketing surveillance of antiretroviral agents.

Post-marketing Surveillance of Antiretroviral Drugs

DR. PIAZZA-HEPP: I am with the Division of Pharmacovigilance and Epidemiology, and we work closely with the Antivirals Division to deal with post-marketing surveillance of adverse events.

I am first going to give a general review of our process, and then I will provide some specific examples of issues that have been under recent evaluation.

[Slide.]

The reporting of adverse events by health professionals in the U.S. is a voluntary process, and health professionals can report these adverse events either directly to the FDA or through the manufacturer. The manufacturer, in turn, is required by regulation to report any adverse events of which they are aware on to the FDA.

[Slide.]

Direct reports represent 10 to 15 percent of all the reports we receive. The FDA has a MedWatch program which was instituted in 1993, which has four goals that I have listed on this slide.

Basically they are trying to increase the awareness of, and the reporting of, drug and device-induced

disease, to make it easier for health professionals to do this, and to provide also regular feedback to the health care community regarding newly discovered safety information.

[Slide.]

The manufacturer reports do represent the bulk of the reports that we receive. Currently, the regulations that govern this reporting is being rewritten, and this is in order to achieve, for one, international harmonization. There have been a lot of guidances and standards developed under the International Council of Harmonization, and we are trying to incorporate those into our rewrite of the regs.

Also, the new regs will stress getting information to produce higher quality reports than we are receiving currently with most of the focus on getting this type of information on those reports with a serious outcome.

In addition, the electronic submission of reports will be required under the new regulations.

[Slide.]

Spontaneous reporting systems do have some limitations. Under-reporting is assumed, reporting biases

exist, and, of course, the exact denominator is not known. So then spontaneous report numbers themselves cannot be used to determine the incidence of an adverse event.

Also, like I mentioned, the information that we received on the individual case reporting forms is often incomplete.

[Slide.]

The advantage of a spontaneous reporting system is it is a signal generation system, and it provides an early detection method of events that were not seen in clinical trials.

One or more reports that we receive can trigger a further evaluation of a particular safety issue. Some other things that might stimulate us to further pursue a safety issue might be literature reports or outside inquiries, something going on in another country. Basically, there is no limit to the things that cause us to initially look into an issue.

We then start looking for similar cases, and we look, first of all, in our Adverse Event Reporting System, which is our Adverse Event database. Also, we have access

to the WHO database and occasionally go to that, and then we search the literature.

Once we do this, we look at the case series as a whole and try to identify trends, possible risk factors, and then assess, well, what does it look like as far as the overall clinical significance of the safety issue.

[Slide.]

For certain selected adverse events, we can do an epidemiologic analysis, and just a few of the things that we participated in, one thing we can do is look at the reporting rate utilizing the drug utilization data that we have access to and then compare our reporting rate of an event against the occurrence rate of that particular disease or event in the population, and with a disease state such as HIV, we would also attempt to further look to see in an HIV population not exposed to a question what the expected occurrence rate might be.

This is usually only useful if the reporting rate is close to or exceeds the expected.

The FDA also funds cooperative agreements which can mainly be described as epidemiologists in the health

care community with access to large health plan databases, and our cooperative agreements are currently investigating several protease inhibitor issues including hyperglycemia, hypercholesterolemia, fat redistribution and cardiac events.

Also, our medical epidemiology staff works with the Review Division to help coordinate possible further study of these events either using the tools that are available to the FDA or in cooperation with the manufacturer.

[Slide.]

The regulatory action that is decided upon is in the purview of the CDER Medical Review Division, and this can be simply a labeling change, which is probably the most common action. A "Dear Doctor" letter or "Dear Health Professional" letters are reserved for the more clinically significant types of events, otherwise, there would be desensitization to such letters.

Sometimes it is decided that the most appropriate action would be to restrict the use of a drug. The most extreme is suspension of marketing, although we have seen a few examples of that lately, and sometimes even if some of

the above actions take place, it is decided that the issue also deserves further study to further clarify the nature of the event.

[Slide.]

We try to achieve public dissemination of the safety information, and one way is the "Dear Doctor" letters. Also, our MedWatch program has an Internet home page where the "Dear Doctor" letters are posted immediately, and the labeling changes are summarized monthly by the MedWatch personnel and posted.

There is also the MedWatch Partners program. What this is, is over 120 organizations representing health professionals and industry, and the partners work with the MedWatch program to encourage their membership to report, and also they receive the safety information which they can then use in any way, shape, or form they wish to in their newsletters or other ways to help inform their membership of these new safety issues.

We occasionally publish our case series and other information in medical journals, and also everything in our adverse event database is available to the public through

Freedom of Information.

[Slide.]

So, some examples I wanted to present are three selected adverse events regarding the protease inhibitors, and the first being--

[Slide.]

--protease inhibitors and bleeding in patients with hemophilia.

[Slide.]

In July of '96, a "Dear Healthcare Provider" letter was sent, and this described 15 case reports of spontaneous bleeding episodes in HIV-positive patients with hemophilia receiving protease inhibitors.

At that time, all the cases were foreign, but we still felt it was important to inform the U.S. healthcare community regarding this event. There were 11 hematomas, 5 hemarthroses, no deaths. It was stated in the letter that the causality was unclear, and the overriding message was that hemophiliacs on protease inhibitors should be monitored closely for spontaneous bleeding.

[Slide.]

This is what is in the current labeling, which does reflect the information that we have to date. We just highlighted a few of the salient points. Basically, it states that we have received reports of spontaneous bleeding in both hemophilia A and B, that in some patients additional factor VIII was required, and that a causal relationship has not been established.

[Slide.]

We do update these issues from time to time, and we took another look at this issue in March of 1998. At that point, we had 82 cases with the four drugs, 87 percent were male. We now do have domestic cases, 62 percent of our cases are domestic, and one of the interesting things is the reporting pattern of this particular event.

We received the bulk of our reports in 1996 just prior to, and several months after, the July 8, 1996 "Dear Doctor" letter, and then in all of '97, we only received 9 reports, and as of March of '98, we had no reports reflected in our database, although we have received a few since.

There is now one death in our series from hemoptysis, and the median onset of this event was 22 days.

[Slide.]

This slide just gives you a listing of some of the sites of bleeding, but basically, they were numerous, and I have listed the sites that involved five or more reports. The most frequent was joints following by skin, muscle. We also had some reports of intracranial or cerebral bleeding, and hematuria where there were no kidney stones present.

[Slide.]

I just made a note that in the literature, there have only been two citations that I am aware of. They are both foreign and they are both anecdotal, representing a total of six case reports.

[Slide.]

The second issue I was going to address is protease inhibitors and hyperglycemia.

[Slide.]

The Public Health Advisory was issued in June of '97. At that time we had 83 cases, and they were described as new onset diabetes, previous history of diabetes with loss of control, and also hyperglycemia.

Five of those had diabetic ketoacidosis, and some

of those ketoacidosis cases have no history of diabetes. Many of the cases were confounded by previous medical conditions or drugs, and we had reports for all protease inhibitors, and again the causal relationship was not established.

[Slide.]

Again, we have highlighted the current labeling for all the protease inhibitors. There is a section under Warnings. I have highlighted a few of the salient points - the fact that this is new onset diabetes, exacerbation of pre-existing diabetes and hyperglycemia have been reported, that initiation or dose adjustments of insulin or oral hypoglycemic agents was required, and also in some cases, diabetic ketoacidosis has occurred.

We don't know what the estimate of frequency is and also the causal relationship has not been established.

[Slide.]

Five months post "Dear Doctor" letter, we had a total of 230 cases, 26 of which were foreign, with the four protease inhibitors, 77 percent of those were male, and the mean age is 43. The mean onset to the event was 101 days.

Only 17 percent of 230 cases had a stated history of diabetes, and another 13 percent had a family history of diabetes.

[Slide.]

Some of the clinical characteristics of these cases included hyperglycemia in 96, new onset diabetes in 94, and previous history of diabetes with loss of control in 40. Diabetic ketoacidosis occurred in 24 of those cases, and only 3 of the 24 of the cases did contain information that indicated they had a previous history of diabetes.

[Slide.]

The literature contains three citations, and again they are all anecdotal case reports representing 13 patients, and none of those are diabetic ketoacidosis.

[Slide.]

The final issue that I will address is also the most recent and active issue that we are currently considering, and that is protease inhibitors and fat redistribution.

[Slide.]

As of March of '98, we are aware of 64 case

reports captured in our database with the 4 protease inhibitors, 66 percent of those are male, and the mean age is 42. The mean onset was a bit longer than the hyperglycemia events. The mean onset in this particular situation was 5.6 months. Some of the major clinical characteristics of those cases included buffalo hump in 15, also central obesity. We had some cases with both peripheral wasting and central obesity. Some reports simply described as "Cushing's" or "Cushingoid," although in the reports that provided such information, Cushing's disease was ruled out by laboratory means.

Some had the buffalo hump with central obesity, so we are seeing all sorts of things, and also some of these patients also had a concurrent complaint of breast enlargement.

We have some pictures to show you.

[Slide.]

This particular patient is a 58-year-old male, and he had been receiving indinavir for four months when he started developing a peripheral loss of subcutaneous fat and also development of central obesity, and a buffalo hump.

This is the photograph of his buffalo hump, which he did have it debulked surgically.

Now, this particular patient also had a history of CHF and history of CAD, and four months after he had this debulking, he did die of myocardial infarction. This is the only death we have among the 64 patients.

[Slide.]

This is a 57-year-old female and also she coincidentally had been on indinavir for four months, and she developed both a central obesity and a buffalo hump.

Both of these patients had had a normal 24-hour urine cortisol, and both of these patients also exhibit a hypertriglyceridemia.

[Slide.]

As you all know, this issue has had a remarkably high interest. It has been a notable topic at recent AIDS meetings, both at the Fifth Conference on Retroviruses and Opportunistic Infections in Chicago in February, and also at the Twelfth World AIDS Conference in Geneva.

The literature has put out quite a bit since last fall. Actually, this is even outdated already. I have

listed two anecdotal reports representing six total cases and four small studies. In addition to this, Dr. Carr's group in Australia published in the Lancet on June 20th a proposed mechanism for this effect, and I have just been informed this morning that Clinical Infectious Diseases contains a few articles in July's issue, and I haven't had a chance to look at those yet.

I have just listed some of the citations. If you don't have those in your handout, I can supply those after the meeting.

[Slide.]

The issues raised among these meetings and the literature are various. One is what is the incidence in protease inhibitor users. Also, is this a unique effect of protease inhibitors or is it just something that has not previously come to light and has always occurred with other antiretroviral agents.

Also, what is the case definition, should we classify buffalo hump the same as central obesity, and should we lump those also with the cases where just an isolated facial or peripheral lipodystrophy are occurring,

and are the mechanisms the same, and what are the possible mechanisms.

In addition, are there any long-term sequelae. This is currently unknown, and I think all would agree that there is a need for further study.

[Slide.]

In summary, then, the evaluation of drug safety doesn't end at approval, it is a continuous process, and the Division of Pharmacovigilance and Epidemiology works closely with the Division of Antiviral Drug Products to monitor the safety of antiviral agents through report and case series evaluation, through literature evaluation, and through coordination of further study by the FDA and/or the manufacturer.

DR. BIRNKRANT: Thank you very much.

Are there questions for Dr. Piazza-Hepp regarding the post-marketing surveillance system? Dr. Bertino.

DR. BERTINO: Two questions. Having just had the pleasure of filling out an adverse drug reaction form, is the MedWatch form on your web site, you could just fill it out on the web site, and E-mail it to you?

DR. PIAZZA-HEPP: I would like to say it should have been by now, because they are piloting it. They have a new method to report on the Internet, where you can just fill out the information. You will get a copy of it, and then that data gets beamed into our reporting system, and it is submitted electronically to us.

They are piloting that program at several hospitals right now and getting the bugs out of it before they release it for general use, but that is definitely coming real soon.

DR. BERTINO: If you have not used one of these forms, I had a pharmaceutical rep present me with the form, I filled it out, sent it to the company. They sent me back another form that essentially asked for all the same situation in a different form.

So, I wrote on it, "I already filled out all this information and sent it back to the company," and I got a letter saying thanks.

DR. PIAZZA-HEPP: In the new regulations, we are trying to give the company some better guidelines on how to conduct followup, because right now the regulations, quite

frankly, it is fairly general.

DR. BERTINO: Another question I have for you, and this really is not so much in the realm of post-marketing surveillance, but FDA has had its fingertips these huge NDA databases, and we will get questions, for example, on our consults about patients on X, Y, and Z, and they have got this, their hair is falling out, they have got a fever, they have got a bad taste in their mouth, whatever, can these drugs cause this.

When you call the manufacturer, at least what in my experience I have found is that their drug information sections cannot access the NDA databases, and I can get this information from the FDA under Freedom of Information if I know what to ask for or what pages I am looking for, and it's a dime a page or something like that.

But it would be very useful, because you have a numerator and denominator in the NDA, in the studies leading up to filing for approval, to be able to access that information, and if FDA doesn't have the time or the personnel to look at those things, it would be nice to make them more easily available to scientists out in the public

domain to be able to do that.

I think a good example is, for example, with quinolones, most of us who work in antiinfectives know that women have about twice the CNS and twice the GI side effects as men do at the same doses, but that is very poorly documented in the literature. That would just be an example. That would be an enormous benefit to be able to access those NDAs.

DR. BIRNKRANT: The medical reviews and the other reviews that comprise the total NDA review will be available on the web site, the FDA's web site.

DR. PIAZZA-HEPP: Also, I just wanted to comment that the safety information from the NDA is very carefully reviewed, and hopefully, the right things go into the labeling in the first place.

DR. BIRNKRANT: Dr. El-Sadr.

DR. EL-SADR: I am wondering if you went back to the studies that we use to approve these protease inhibitors and with the hindsight now, did you try to go back and see how many episodes of hyperglycemia, if this was at all described.

DR. PIAZZA-HEPP: Yes.

DR. EL-SADR: Is this all if it?

DR. PIAZZA-HEPP: That is something, not only with the antiretroviral agents, but this is typical. Once it was considered an unexpected event, comes up after the drug is approved, it is pretty common that the Review Division takes a look back again just to make sure they didn't miss something, so that they take another look at the data they reviewed in the first place just to make sure that there wasn't something that was overlooked.

Oftentimes it is not something overlooked, it is just that maybe the frequency of the event wasn't at, you know, large enough to be able to be picked in clinical trials, but that is something that has been done.

Jeff, did you want to comment further on that?

DR. MURRAY: Yes. I mean we always get very nervous when we finds something. I mean I am always--that is the first thing I do is look back and say, oh, my God, what did I miss. But for hyperglycemia, for example, three out of the four protease inhibitors in the NDA or in follow-up supplements that the NDA had maybe one, not more than one

case of hyperglycemia, and when you get one case of anything, you know, hyperglycemia or something that occurs naturally in the population, you don't necessarily know what to make of it.

Now, in hindsight, you can say, well, that case might have been one, but there was not enough of a signal.

DR. HAMMER: This drives to the point of the followup, I think, in many of these studies for which drugs have been approved. For example, ACG320, we looked at it, but, in fact, the medial followup was 38 weeks, and we saw no difference in hyperglycemia or new diagnoses of diabetes and reported that, but I think this, as well as lipodystrophy are issues that were perhaps missed by the short followup, but also I think the lipodystrophy, there probably were cases that physicians just did not recognize. It is clear the more you look for that, the more you see it.

DR. BIRNKRANT: Dr. Pomerantz.

DR. POMERANTZ: Obviously, the endocrine changes and the fat distribution changes are fascinating with the protease inhibitors. Some children have received protease inhibitors. Has the FDA received any reports of what

protease inhibitors may have doing to the pediatric population that has received it when it comes to endocrine abnormalities?

DR. PIAZZA-HEPP: Well, a few of our 64 cases are in children. A couple of them are described as either an exacerbation of what was beginning to look like something kind of cushingoid or more, just kind of--or Cushing's or cushingoid type event.

As far as that being looked at prospectively in studies, Jeff?

DR. MURRAY: Not looked at that prospectively yet in pediatric studies.

DR. BIRNKRANT: Dr. Feinberg.

DR. FEINBERG: Just to underemphasize this issue of the necessity for long-term followup once again, I will report to you that anecdotally, we feel we are seeing more and more cases of change in body habitus as you get into the second year of therapy.

I know that what was just presented here said something like five months is the average, and I think we will only really know what all of this means, as well as

whether there are implications for cardiovascular health if we provide long-term followup in an organized way, just not adverse event report, but I mean studies that long-term followup.

Since some of us offer treatment to seroconverters, this is not a small, it is not even the people with 500 or 600 T cells, but to seroconverters, this is not an issue of small dimensions, because you really are saying to people they are going to be treated for an extraordinarily long time.

DR. BIRNKRANT: It is a very important issue, it is under continuous review, and labeling will be updated, and it is an evolving, ongoing, and continuous process. As Toni said, once a drug is approved, the safety monitoring doesn't stop, it continues.

DR. HAMMER: I would just emphasize one point in the next to the last slide under Issues for the fat redistribution syndrome, trying to come up with a practical early case definition, knowing that it may be modified, definition or definitions is very important, more important in some areas than others, certainly very important in the

fat redistribution syndrome for which there is controversy as to whether this is all part of the same thing or different things, and we see some of the lead investigators in the world arguing about the case definitions, the incidence, and whether it is PI-specific or antiretroviral therapy-specific.

So, case definitions where the agency can help bring groups together to have working definitions for clinicians and trialists would be, I think, very helpful.

DR. BIRNKRANT: We will follow through on that.

Dr. Lipsky.

DR. LIPSKY: In reference to the data where you are getting the reports from, I think it is like 14 percent from spontaneous reports, and the rest from industry. Do you consider MedWatch a success or what can be done to make it a better success?

DR. PIAZZA-HEPP: The MedWatch program encourages since they have begun, we always accepted direct reports, but since the MedWatch program has begun, they have tried to emphasize the receipt of serious reports, and even though their overall percentages haven't really increased as far as

percent of reports received directly, the number of serious cases proportionally has increased. I mean we don't just get a lot of non-serious rash cases with Bactrim like we used to. The reports seem to be more significant than they were.

Also, the quality of the reports is better, the quality of direct reports. We seem to be getting more complete information in the direct reports. Also, the program emphasizes reporting, but they emphasize reporting to either the FDA or the manufacturer. They just want health care professionals to report, stating that yes, you can report directly to the FDA, but you can also report to the manufacturer.

So, it is hard to say, because of those factors, you know, what the overall impact is. Believe me, the MedWatch program would like to have seen it gone from 15 percent to 50 percent or whatever, but we still do encourage reporting through the manufacturers, and I am sure the manufacturers would be happy about that.

DR. MURPHY: I just wanted to follow up on her comment. I think that one of the great things about

MedWatch is that the physician who fills the form out or the health care providers is providing us more data than we sometimes get otherwise, and one of our issues is that when we get AEs sometimes from the sponsors, it will be two lines, and they have a process for following up, but it is usually sending a letter as their first step unless it's a serious, a really highly serious event.

So, this facilitates the process, you can imagine, if we get quality information right up in the first part of the process.

DR. BIRNKRANT: Dr. El-Sadr.

DR. EL-SADR: I am just curious when we report to the manufacturer, I mean often you call about an issue. I mean are they--you call an 800 number and you speak to a medical person, are they then required to generate something to the FDA based on that conversation?

DR. PIAZZA-HEPP: Yes. If you indicate that--

DR. EL-SADR: You have to say I think it's an adverse event or you can just have a conversation?

DR. PIAZZA-HEPP: That is actually a common route that manufacturers get reports. You have health care

professionals calling in trying to get information from the manufacturer because they have a patient on drug X, and they have experienced a certain event, and you don't necessarily think it is caused by drug X, but you are suspicious and you want to know if they have any information. Well, that does become an adverse event report, because you wouldn't have called in the first place if you hadn't suspected at least that there could be a possible relationship.

DR. BIRNKRANT: We are also in contact with regulatory agencies throughout the world, as well, to keep an eye on what is happening in other parts of the world, as well.

Other questions for Dr. Piazza-Hepp?

I would like to thank everyone, both speakers and panel, for an interesting morning session. The afternoon session will begin at approximately 1 o'clock. Thank you very much.

I am sorry. Open public hearing. Anyone signed up?

Open Public Hearing

DR. HAMMER: There is no one signed up for the

open public hearing, but it is an opportunity if anyone present wishes to make a statement, please come to the microphone and identify yourself.

[No response.]

DR. HAMMER: Seeing no immediate rush to the microphone, I will declare this session closed. Thank you.

[Whereupon, at 11:35 the open session was adjourned.]

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