DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ARTHRITIS ADVISORY COMMITTEE

Monday, July 29, 2002

8:00 a.m.

Holiday Inn Bethesda
Versailles I and II
8120 Wisconsin Avenue
Bethesda, Maryland

PARTICIPANTS

Gary S. Firestein, M.D., Chairman
Kathleen Reedy, R.D.H., M.S., Executive Secretary

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Kenneth D. Brandt, M.D
Leigh F. Callahan, Ph.D.
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Yvonne S. Sherrer, M.D.

GUESTS

ARTHRITIS ADVISORY COMMITTEE

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Raymond A. Dionne, D.D.S., Ph.D.
Janet D. Elashoff, Ph.D.
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Nathaniel P. Katz, M.D.
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NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

Frank F. Davidoff, M.D.
Alastair Wood, M.D.

INDUSTRY REPRESENTATIVE

Charles H. McLeskey, M.D.

GUESTS

David Borenstein, M.D.
John T. Farrar, M.D. MSCE
Vibeke Strand, M.D.

C O N T E N T S

C O N T E N T S(CONTINUED)

P R O C E E D I N G S

Call to Order and Introductions

DR. FIRESTEIN: Welcome to everybody to this meeting of the Arthritis Advisory Committee along with a number of esteemed guests.

My name is Gary Firestein. I am the chair of the committee. Before we get started with the actual agenda, because there are so many new people here today, it might be valuable to go around and have everybody around the table introduce themselves briefly.

As I said, I am Gary Firestein. I am from UC/SD and I am a rheumatologist.

Why don't we go around to my left.

DR. SHERRER: I am Yvonne Sherrer. I am a rheumatologist. I am from Fort Lauderdale.

DR. CUSH: Jack Cush. I am a rheumatologist from Presbyterian Hospital of Dallas.

DR. CALLAHAN: Leigh Callahan. I am an epidemiologist from the University of North Carolina in Chapel Hill.

DR. WOOD: I am Alastair Wood. I am a clinical pharmacologist from Vanderbilt.

DR. DAVIDOFF: I am Frank Davidoff. I am

an internist and a recovering journal editor.

MS. McBRAIR: Wendy McBrair. I am a nurse and health educator from Virtua Health in New Jersey.

DR. WOOLF: Clifford Woolf. I am a biologist from Massachusetts General Hospital and Harvard Medical School.

DR. DIONNE: Ray Dionne, clinical pharmacologist, National Institute of Dental and Craniofacial Research.

DR. MAX: Mitchell Max, neurologist, National Institute of Dental and Craniofacial Research.

DR. WITTER: Jim Witter from the FDA.

DR. SIMON: I am Lee Simon, Division Director of 550, FDA.

DR. McLESKEY: Charley McLeskey, an anesthesiologist, serving as the industry representative here from Abbott Labs.

DR. STRAND: Vibeke Strand. I am a rheumatologist, teach at Stanford, and work as a consultant.

DR. BORENSTEIN: David Borenstein, rheumatologist, Clinical Professor at George Washington University.

DR. FARRAR: John Farrar. I am a neurologist interested in pain management at the University of Pennsylvania.

DR. ELASHOFF: Janet Elashoff, biostatistics, Cedars-Sinai and UCLA.

DR. ASHBURN: Michael Ashburn, anesthesiologist, from the University of Utah.

DR. ANDERSON: Jennifer Anderson, statistician, from Boston University Medical Center.

DR. KATZ: Nathaniel Katz. I am a neurologist at Harvard Medical School.

DR. MANZI: Susan Manzi. I am a rheumatologist from the University of Pittsburgh.

DR. ABRAMSON: Steve Abramson, rheumatologist, NYU and Hospital for Joint Diseases.

DR. KATONA: Ildy Katona, pediatric rheumatologist, from the Uniformed Services University.

DR. BRANDT: Ken Brandt. I am a rheumatologist from Indiana University.

MS. REEDY: Kathleen Reedy, Food and Drug Administration.

DR. FIRESTEIN: As I mentioned, we do have

a very full schedule and we have a large number of people in this committee today, so it will be impossible for everybody to take the podium for prolonged presentations, and I would just ask the members of the committee to try to keep comments to the point, so that everybody can have an opportunity.

We will begin the meeting with a meeting statement read by Kathleen Reedy.

Meeting Statement

MS. REEDY: This is the meeting statement for the Arthritis Advisory Committee meeting on July 29th and 30th, 2002.

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 Food and Drug Administration has approved general matters waivers for the following special government employees which permits them to participate in today's discussions: Gary Firestein, Kenneth Brandt, Ildy Katona, Yvonne Sherrer, Susan Manzi, Jennifer Anderson, John Cush, Alastair Wood, Nathaniel Katz, Michael Ashburn,

Janet Elashoff, Mitchell Max, Raymond Dionne, Steven Abramson.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, Leigh Callahan, Frank Davidoff, Wendy McBrair do not have any current financial interests in pharmaceutical companies, therefore, they do not require a waiver to participate to today's discussions.

We would like to note for the record that Ms. McBrair's employer's interests in two drug companies are exempt under 2640.203(g).

The topics of today's meeting are issues of broad applicability unlike issues before a committee in which a particular product is discussed, issues of broad applicability involve man industrial sponsors and academic institutions. The committee participants have been screened for their financial interests as they may apply to the general topics at hand. Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member, consultant, and guest.

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

We would like to note that Dr. Charles McLeskey is participating in today's meeting as a non-voting industry representative. As such, he has not been screened for conflicts of interest.

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

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

DR. FIRESTEIN: Thank you very much.

Now we will move on to the Welcome from Dr. Simon.

Welcome

DR. SIMON: Thank you, Gary, and I would like to welcome the committee. We are grateful that you are willing to come, take time out of your

practice and busy days to join us here in this rather hot and humid land, but nonetheless, the fact that you have been able to take time out Monday and Tuesday, we are quite grateful about.

We recognize that much of what you do here is done involuntarily and we recognize that that is a burden and the government appreciates your commitment.

Having been recently on the other side of this microphone and having sat around the table with you as a committee member previously, I can appreciate really what it takes to do this, so thank you.

I want to make clear that this meeting is the first of many meetings in an iterative way for us in 550, and hopefully other divisions in the future, to participate with you all in discussing issues of pain, which we find a very critical time in the development of new therapies for pain.

We have advanced the science of understanding mechanisms and we believe that part of our role at the FDA is to foster new therapeutic development by discussing all different kinds of ways to look at pain indications and how one would approve such drugs. We believe that these kinds of

discussions will allow us to further understand better how to create and construct guidances for industry.

Much of what we will discuss today will not, and has not, been generally discussed within the entire FDA. I would like to make clear that much of the discussion will inform us in 550, the Analgesics Anti-inflammatory and Ophthalmologic Product Division, about issues that we have been grappling with and have been advising industry about, about the products that we are responsible for.

However, much of what we will discuss today will be brought back for further discussions with other divisions, such as 170, Anesthetics and Critical Care, that is particularly interested in this topic since they are responsible for drugs like opioids.

So, we feel very strongly that today's discussion, although not directly product oriented, will help us and inform us significantly about where we are going in the future in guidance development.

So, again, thank you very much, and I will turn the meeting back to Gary.

DR. FIRESTEIN: Thank you, Lee.

We will move ahead now with an introduction to the topic from Dr. Witter.

Introduction

James Witter, MD., Ph.D.

DR. WITTER: Good morning. Thank you, Gary, Dr. Simon.

I am the clinical team leader in 500 and, as such, I would like to thank the members of the team that have spent a lot of time and energy getting ready for today. I particularly would like to acknowledge the help of Barb Gould and I think you will appreciate some of her work here shortly.

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In case you missed it, we are here to talk about pain, and pain is one of those words that even, standing alone, evokes an emotion out of I think everybody. Maybe, in fact, some of you have some of this right now. It is generally not a good emotion, though.

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Pain is really quite fascinating because it is, in one way, the ultimate symptom and therefore, the target for drug development, which is part of the interest today, but it crosses some

magical line and can become a disease, which we talked about at a meeting just down the street a couple of months ago. So, it kind of goes through what we might think of as I guess a phenotypic change.

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The purpose of the meeting really, then, is what we are going to try and do is simplify things down to concepts and really examine two main aspects of pain and its relief. One of those is how have analgesics been studied and labeled to date, and how should analgesics be studied and labeled in the future.

The ultimate goal, then, is to inform analgesic labels in a meaningful way for both patients and clinicians. So, a lot of the focus is going to be a discussion of labels.

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Let's starts off with some definitions then. Can we say, then, that since acute pain is generally considered a self-limiting condition, that that should inform us on how the drug should be studied, labeled, and used? Use is what we are particularly concerned about because we know that off-label use has resulted in serious adverse

events and death with certain analgesic drugs in the past.

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Can we, on the other hand, say that chronic pain is defined as daily or intermittent pain that occurs either on or off medication and lasts more than 3 months for patients who do not have cancer, but lasts more than 6 weeks for those who have cancer, if what we are trying to do is recruit patients into trials, we don't want to keep them out, particularly those that have cancer.

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So, I am going to ask you to answer a series of questions in your head. Please don't raise your hand unless they apply.

But I would like to know: Who has never experienced pain? Who thinks that pain doesn't hurt? Who thinks that pain doesn't interfere with your activities? And who thinks pain doesn't impact your life?

I see no hands.

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So, do we then have an agreement, unspoken, that an analgesic should: relieve pain, should improve function, should improve quality of

life, and do so in a safe manner?

And this is important. The other side of the equation from working is safety, and we are going to talk about that today and tomorrow also, but it is always going to be I think in the back of our minds.

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As I mentioned earlier, we are really going to be focusing on labeling, so if you look in the draft OA or in the RA guidance document, you will see something that states the following: "Although label claims have legal and regulatory uses, their central purpose is to inform prescribers and patients about the documented benefits"--and I have inserted in here (and risk)--"of a product."

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Now, this isn't the first time that we have talked about labels and analgesics. We did so about four years ago. We took only one day, and I think by the end of tomorrow, you will realize that that was not sufficient. We broke it up into a morning and afternoon session, and I think I see some people that were here then.

The morning session, we really discussed

the onset of pain relief, what we call fondly, internally, the "fast-faster" wars, and we also studied design of Rx prescription/OTC analgesics.

In the afternoon, we devoted it to pain claim structures for both acute and chronic pain.

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We asked some questions, as we usually do, of the Advisory Committee. We asked: Should pain claims be categorized as: for acute versus chronic versus unrestricted or I guess general pain claims? Should they be by categories, for example, neuropathic pain, or should they be by subcategories, for example, diabetic neuropathy?

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We also then asked: Of these studies, how many should there be, how long should they be, what kind of pain "models" should we be using to inform such labels, and what is this concept of "clinically meaningful" benefit and how should it be determined in both the setting of acute and chronic pain?

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But we are here to talk about the future, so what we are going to be discussing throughout these two days are some ideas about how to move

forward and how to make pain claims for the future, and what we might able to do, for example, is break them up into two basic categories, a clinical and a mechanistic.

Clinical is first because, as I mentioned before, pain is the ultimate symptom, so we need to make sure that we address that. Tomorrow, in particular, we are going to be discussing the acute pain setting and, in particular, what we have called the ABC's of doing studies to look at analgesics in the acute situation.

Later today, we will be talking more about chronic and what those studies should be, in particular, then labels that should have a specific chronic claim, such as osteoarthritis, which we routine give out in the division, or should we talking about more general claims, replicates of three models, which Dr. Simon will be going into in just a bit, but I think one thing that Dr. Simon is going to stress is that we are trying to set up many ways, particularly for chronic pain, many ways to get approved.

Then, I think we are going to be discussing some mechanistic approaches or what we might call some bridging studies, and I will talk

about that in a bit.

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So, let's just stop for a moment and think about a mechanistic claim. We don't have such a thing, but we wonder what it might look like if we did have one, would it look like, for example, something that would say prevents neuroplasticity, does that make sense to people, or reducing prostaglandin levels, or reducing substance P in CSF, are those the kinds of things that we would mean by a "mechanistic claim."

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So, mechanisms, I have come up with something here called "Mechanisms of Total Pain Relief," and this is a hypothetical model--and please blame me for anything that is wrong here--but let's just say that we can categorize things in terms simply of we will call them Factor X, which are NSAIDs, and like-related compounds, Cox-2's, for example, and let's take a Factor Z, which are opioids and related compounds, tramadol, for example, and then Factors Y, which are future drugs either in development or still in somebody's mind somewhere.

Let's say that these then contribute to

this called chronic pain.

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If we do some mathematics on this, can we say that--let's form some hypotheses here. Can we say Hypothesis 1, for example, that if you take any X or any NSAID, and you add that to any Z or any opioid, you will get 100 percent pain relief, is that the correct hypothesis?

Or is it, Hypothesis 2, that we take any combination of X and any combination of Z, we have to add in something else, something else that is missing, the Y factor, to really get 100 percent pain relief?

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Now, once we have answered or tried to answer that, then maybe we then have developed a plan for everybody. Plan 1, for example, going back to Hypothesis 1, would be, well, we really have all we need out there. All we need to do is improve the safety of these existing compounds.

Or do we say Hypothesis 2 is true, and sure, of course, we want to optimize use of existing drugs, but what we really need to do is develop and improve new drugs.

If that doesn't work, we have an

alternative plan and we are ready to go here, we have the extra strength pain relief--and thank you, Barb.

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So, I think it is important, the ideas that we discuss today, they sift down, they eventually become drugs. They get into research, both pre- or non-clinical and clinical. If they are lucky, they come to us. If they are lucky again, they get labeled and they get out there for use.

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We are very much a part of this process, and we have become more so thanks to the help of Dr. Meyer Katzburg, who I would like to acknowledge for all his work in setting up what we now have as we are live on the air. The Division has a web page accessible through--go to the CDER web site. You will see there is an announcement of this web page. We are excited about it, it is still growing, and we would love your comments. I can assure you what you send to us, we will all read it, so make it good.

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A couple of months ago I had the pleasure

and pain experience to work with Dr. Dionne, who is sitting here today, on the NIH-FDA Analgesic Drug Development Workshop.

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We had some objectives for that workshop. We wanted to define pain in terms of the unmet needs for pain management and where to go for unmet needs in terms of pain research, and we discussed how to harness the emerging technologies and improve the development and ultimate FDA approval of new therapies.

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Of course, we had some outcomes and suggestions from this. There was a concern that this separation of pain into acute and chronic may miss addressing the nervous system "plasticity" that many feel goes on.

It was acknowledged that there is no consensus for a pain metric, but that one, in fact, needs to be developed to allow for comparisons and poolings of results across the analgesic trials.

There was a lot of discussion as to whether new analgesics need to be evaluated as supplementary medications on existing ones because that represents more accurately the pattern of

clinical use.

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We talked about the need for new therapies to treat pain mechanisms and we talked about how to translate these scientific advances into improved pain relief when it comes down it, it is going to really take a cooperative effort between academics and industry and the regulatory agencies, such as us.

Then, we talked about the FDA guidance of 1992 and how it needs revision. Let me just talk about that. Dr. Fang will be discussing it in much more detail.

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Let me just mention to you, so that we are on the same page, that the document really discusses analgesic approaches in the 1980's, and if you read it, it assumes that revision would be necessary with time, so I think we all are in agreement that we have arrived.

Maybe one of the most distressing features is that it encourages "me too" types of drugs rather than encouraging the "me first" types of drugs that I think we all agree we need in the future.

So, without further delay, I would like to introduce Dr. Christina Fang from the FDA.

I have omitted here, my mistake, I am sorry, Dr. Sharon Hertz, also from FDA, will be discussing the '92 guidance document and some of the positives and negatives from that.

We will have Dr. Clifford Woolf from the Mass. General talk to us about the issue of plasticity, our own Lee Simon, who will be discussing the pain claim structure, and Dr. Borenstein will talk to us about what might be one of those new indications in particular lower back pain.

Thank you.

DR. FIRESTEIN: Thank you very much.

As you noted, we are going to move ahead. If the FDA is going to revise the 1992 guidance, it might be useful to first review what they are.

So, Dr. Christina Fang and Dr. Sharon Hertz will do that now.

1992 Guidelines

Christine Fang, M.D.

DR. FANG: Good morning. My name is Christina Fang. I am a medical reviewer for the Division of Anti-inflammatory Analgesics and

Ophthalmic Drug Products.

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I am going to talk about 1992 analgesic guidance document and the current issues.

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The 1992 Guideline for the Clinical Evaluation of Analgesic Drugs had provided the guidance to analgesic drug development and the research in last 10 years. It was originally developed with the focus on NSAIDs and opioid type drugs.

With the emerging new molecular entities and with our growing knowledge about analgesics and analgesia, we see the need to resolve many major issues.

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The major areas for improvement in 1992 guidance document will be presented at the subsequent slides. Each will be followed with a brief discussion on major issues.

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The 1992 Guidance document recommended the analgesic indications to be for the management of pain. It is stated that evidence of pain. It is stated that evidence of pain of several different

etiologies will justify general purpose analgesic labeling, also the inclusion of specific labeling indications for preoperative medication, for support of anesthesia, for obstetrical analgesics, or the dysmenorrhea requires specific studies.

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How general and how specific the indications should be has always been in debate. The indication recommended should be based on the number of acute and chronic pain model studies.

All the analgesics should be studied sufficiently to include representative subpopulations of major types of pain. The purpose is to provide guidance to practitioners and to minimize unsafe and ineffective off-label use.

In terms of specific indications, there are some limitations. For example, we are not able to study all of the indications because of the lack of model sensitivity. If a drug only works for very specific indications, it should be demonstrated that the drug has unique pharmacodynamic activities directed only at the specific indication.

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Acute and chronic indications. This topic

has always been in debate, as well. We see the need to study the short-term and long-term efficacy, but how much should we have regulatory requirement in terms of models, in terms of replications, we see the same model and the different models, and in terms of length of study.

How short-term or the multiple-dose study will help us to study the initial dosing regimen to see if loading dose is necessary and to determine optimal dosing interval.

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In the discussion of chronic studies, the 1992 Guidance stated that the focus of the multiple-dose studies of more than 2 to 3 days in duration is to provide documentation of clinical acceptability and the safety of the test drug rather than providing pivotal proof of efficacy.

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Today, we no longer think of studies of 2 to 3 days in duration as chronic studies. We need to determine the length for long-term efficacy study. If adequately designed and well controlled, the long-term studies should be able to provide pivotal proof of efficacy.

It is especially valuable for drugs with

delayed onset. The reason we ask for long-term studies is because we see the problem with off-label use for chronic pain. Also, these long-term studies will provide useful information for product labeling, about long-term benefit-risk ratio and the durability effect.

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In terms of pain models, the 1992 Guidance stated that the selection of pain model depends on the strength of analgesia, route of administration, model sensitivities, active controls, and mechanism of action.

Also, the initial Phase II studies should explore a wide enough range of pain models.

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We see the need for more acute and chronic pain models because we only have limited models for study of acute pain and most of which were developed for the development of NSAID type drug and also we have limited models for chronic pain, and most of those to be studied were musculoskeletal in origin.

We also see the need for models to study the worst type of pain because of the dosing regimen that could be different for this kind of

setting, and maybe there is a need for concomitant and rescue analgesics.

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In terms of dosing, the 1992 Guidance stated that Phase II studies "should explore the entire dose-response curve of the test drug and should be the basis for selecting the dose used in later Phase II and Phase III studies."

Phase III studies are "intended to assess the effectiveness of the recommended dosage schedule under conditions of use."

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We see the need for studying both dose levels and dosing intervals at acute and chronic settings. The dosage obtained from acute setting may not apply to chronic use, and the dosing recommendations should be based on optimal benefit-risk ratio rather than dosing many for convenience.

We should also differentiate fixed dosing in clinical trials for establishing efficacy from the variable dosing used in clinical practice.

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In terms of efficacy parameters, the 1992 Guidance stated that, "The development program for

an analgesic should collect data to describe adequately onset of effect, peak effect, and duration of effect. There many ways to collect data on these measures of efficacy."

Then, there is a long list of measured and derived parameters in the 1992 Guidance document.

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The choice of efficacy parameters should be based on minimizing bias, demonstrating time course of effect, and providing useful information for dosing recommendations.

Pain curves, onset, and the duration should all be studied using valid and reliable tools, and should be studied for both acute and chronic settings.

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For chronic pain evaluations should determine how much the pain-related functional status and the patients global satisfaction should be used for primary or supportive evidence.

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In terms of study controls, the 1992 Guidance recommends the placebo and active control for single-dose study, the active control or placebo control with rescue for short-term,

multiple-dose study, and active control for long-term or multiple-dose study.

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We see the need for adequate controls in both acute and chronic analgesic studies. The placebo controls should always be considered whenever applicable because of the high placebo response in analgesic trials.

The superiority design versus equivalence design should be planned accordingly. There are some special considerations for chronic studies in terms of differential dropout rates and in terms of how to keep blinding intact if there are different safety profiles between the drugs to be compared.

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In terms of effect and sample size, the 1992 Guidance stated that the calculation of sample size "depends on the variance, the magnitude of difference to be detected, and the desired power."

Special consideration should be given to the "validity and the implications of the clinical significance of the differences or similarities to be detected."

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How do we determine clinically meaningful

effect size has been a debate. There is no consensus on how to define up-to-date. There are did approaches. Whichever approaches are used, a wide database should be applied. The sample size determination is closely related to the determination of clinically meaningful effect size.

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In terms of safety, the 1992 Guidance stated that for peripherally acting or NSAID oral analgesics, the study should regular dosing for a least 6 months. For centrally acting oral analgesics, there should be regular dosing for at least 1 month, continuing for at least 3 months if feasible. For oral combination analgesics, the studies should have regular dosing for at least 1 month.

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We see the need to study the safety in terms of the relationship between extent of exposure and adverse events. The extent of exposure includes the level of exposure and the length of exposure.

We see the need to study the maximum recommended dosing proposed. The ICH guidelines for chronic pain only provides the minimum

requirement for minimal number of subjects and the length of exposure.

There may be a need to study the representative study population. There may be a need to study the special population with high risks. The large safety trial may be needed if there are serious safety concerns.

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In terms of opioid sparing, we need to determine the clinical relevance of opioid sparing. We need to see the extent of dose sparing that is clinically meaningful.

We need to decide if opioid sparing could be discussed in terms of concurrent analgesics or in terms of adjuvant analgesics. For opioid sparing study design to be treated as a concurrent analgesic, there should be consideration of standardization of opioid use and also the data analysis that combines pain data and the rescue medication data, and we need to determine how to evaluate efficacy and safety for this kind of use.

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You can see we have many issues to be resolved. We need a strong need to updating 1992 Guidance document. We see the need for proposals

for future analgesic research. There is also the need for consensus among researchers, drug sponsors, and the regulatory agency.

Here, I am just introducing the general concepts and the details will be discussed by my colleagues in the subsequent presentations.

Thank you very much.

DR. FIRESTEIN: Thank you very much.

Now we will go to the second half of this presentation by Sharon Hertz.

Sharon Hertz, M.D.

DR. HERTZ: Thank you.

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First of all, I would like to thank Dr. Simon and his division for inviting us to participate in this Advisory Committee. I am from the Division of Anesthetics, Critical Care, and Addiction Drug Products. As many of you may know, we also work with a lot of the analgesic products.

I am going to present some highlights from our internal discussions on analgesics development, and there will be some overlap with Dr. Fang's presentation. I think what may came out is that there is tremendous overlap in the Division's concerns and in a lot of our approaches to this

process.

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The 1992 Guidance has been in use for over a decade and we know that subsequent advances in pain research and in pain management really are calling for new approaches to analgesics development.

The 1992 Guidance places what we feel is an undue emphasis on models rather than on really looking at particular clinical settings of intended use and target populations, and this has led to some ambiguous labeling and perhaps an inadequate exploration of drugs in the context of the actual clinical use.

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We think that the guidance lacks an adequate emphasis on Phase II dose finding and we have seen many development programs that have come through with very abbreviated Phase II programs.

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There is not an adequate addressing of duration of clinical trials, particularly for drugs intended for chronic administration, and study designs that are recommended in the guidance are no longer considered practical and have been shown to

lead to somewhat ambiguous results.

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Selection of adequate control groups, as described in the current ICH guidelines, has replaced some of the older thinking represented in the older guidance.

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While the 1992 Guidance makes a distinction between pain due to inflammatory and noninflammatory conditions, it fails to recognize the greater variability in pain etiologies and how this may impact on the response to different analgesics.

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Here are some of the basic development points that we tend to focus on and request when we discuss program development with sponsors. Obviously, for Phase I, we like to see an adequate characterization of the PK profile, but not just for single dose, but also multiple dose studies.

We like to see preliminary safety and tolerability over a very broad range of doses potentially anticipating what will be used later on.

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During Phase II, we like to see the product explored in potential target populations. Pain conditions identified as responsive in preclinical trials or experience with drugs of a similar class may help define populations to begin exploring during Phase II.

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Analgesics are rarely used only as a single dose agent, so single dose studies shouldn't be proposed for support of marketing applications. Rather, these should be used more to explore early on, analgesic properties.

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We like to see a wide exploration of dosing during Phase II to help inform what would be appropriate arms in Phase III trials.

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Phase II provides a lot of very important opportunity to explore outcome measures and determine what approach is most likely to demonstrate the best way to demonstrate efficacy of this particular product.

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Is there a subgroup that responds well, suggesting a responder analysis is a better primary

analysis? If so, what are the characteristics of that group? Or do most patients exhibit a moderate but important improvement suggesting an analysis of mean scores as most informative?

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Are there products that are already approved that are better than the studied product, so that even though the study drug beats placebo, it doesn't necessarily lend itself to the target population in that study, that there may, in fact, be another, better indication for the product?

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During Phase III, we ask the sponsor to consider ways to prospectively define a clinically meaningful response for the primary pain variables, preferably using validated measures. As Christina mentioned, this is a very difficult thing to do, because we don't necessarily know yet what clinically meaningful represents.

We really prefer the use of validated measures particularly for the primary outcomes.

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For a product likely to be used chronically, we request studies of adequate duration. Typically, we request 12 weeks on final

titrated dose. This affords an opportunity to assess durability and it is a concept, the 12-week concept is also used for other products in other areas of the Agency.

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Also, for our particular drug groups, particularly the opioids, these 12-week studies can offer an opportunity to provide information concerning tolerance if designed accordingly.

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Efficacy needs to be replicated, not necessarily in an exactly duplicated design, but in a similar population, and these studies are going to provide the basis for informing the label and how the product is to be used.

We look forward to getting together with the hosting division to discuss the outcome of this Advisory Committee and to work together on further guidance development and approach to analgesic development.

Thank you.

DR. FIRESTEIN: Thank you, Dr. Hertz.

The next item on the agenda is a discussion of some of the basic science behind pain and analgesia by Dr. Clifford Woolf.

Basic Science

Clifford J. Woolf, M.D., Ph.D.

DR WOOLF: Thank you very much for this opportunity to share a basic science perspective on this very important issue.

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What I would like to try and discuss today is how the advances that have occurred in the last 10 years, since the 1992 Guidelines, some of the advances that have been made and the implications for them in looking at analgesia and analgesics, and this issue of labeling.

Some of the particular issues I would like to address is whether there is a basis for the differentiation of pain in terms of its chronicity, intensity, and how our understanding of the mechanisms that are responsible for pain can drive and may actually be included in any discussion about indication.

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To begin with, to look at pain chronicity, I think it is important, when we look at the difference between acute and chronic pain, to try and identify whether chronic pain may be the results of the persistence of a mechanism or may be

the result of the recruitment of a novel mechanism that is not present in those patients that have acute pain, because these clearly are quite different.

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So, doing a kind of an analysis of those, we can readily appreciate that acute pain characteristically is transient, it may be recurrent, but it is always reversible. That is a key element implicit in our definition of acute pain, whereas, chronic pain, I think we can usefully divide into two very broad categories.

There are those patients who have long-lasting pain which is reversible, so that if the driving mechanism responsible for that pain is removed, that pain will tend to disappear, whereas, there are other patients where the pain is truly persistent and we can even say irreversible.

I think these are very distinct subcategories and we need to recognize and solve that.

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In terms of looking at pain intensity, again, the issue is whether there is a continuum of pain mechanisms that can generate pain of different

intensity divided between mild, moderate, and severe, or whether each of these levels of intensity of pain reflect discrete mechanisms that operate, that are recruited at different levels of disease or as new etiological factors come into play.

Another important aspect we need to take into account is when we look at the intensity of pain that is experienced by an individual, whether that reflects an increase in some stimulus, some external driving force, some disease factor, or, indeed, may be an alteration in the responsiveness of the nervous system.

Certainly, there is now increasing belief amongst basic scientists that the responsiveness of the nervous system can alter quite profoundly, and an increase in intensity may not necessarily reflect an increase in stimulus.

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The simple underlying approach to pain until quite recently was that multiple etiological factors operating by means of inflammation, tissue damage, nerve lesions, or a number of other ways, could act on a highly specialized sensory apparatus in the nervous system to drive the symptoms and

signs that we now collectively call pain, and that there was, if you like, this convergence of etiological factors acting on the nervous system to initiate a set of changes which generated the response that we interpret as pain and that we could then subdivide the pain depending on the etiological factors, the duration, the associated changes into different pain syndromes.

What I would like to argue today is that we need to move away from this very simple model, and I would like to show you why it is neither correct nor helpful in defining the approach the analgesics.

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One of the main reasons is that it has become increasingly clear that we are dealing with multiple distinct pain mechanisms. This is an incomplete list. Almost certainly this list is going to change as our understanding of pain improves, but it is clear that there is a distinct mechanism that is responsible for nociception by which I mean the sensory mechanism that is responsible for pain in response to a transient non-damaging, noxious stimulus.

There are distinct mechanisms that operate

to alter the sensitivity of the high-threshold nociceptive primary afferents that are responsible for nociception, and these changes at the peripheral terminals of these nociceptors are what we call peripheral sensitization and are a major driver of inflammatory pain.

In addition, it is increasingly apparent that changes in the processing of sensory information within the central nervous system, that collectively we can call central sensitization, play a major role in the shaping of the pain experience and may in some individuals and in some situations be a major factor responsible for the pain.

After nerve damage, we now appreciate there is the development of ectopic excitability, sensory inflow with a sensory stimulus. There are also increasing indications that lack of inhibition and structural alterations in the nervous system may play a major role particularly in chronic pain associated with nerve damage.

Today, I am going to stick my discussion to the first three mechanisms and try and illustrate how understanding of them has implications for determining the efficacy of

different groups of analgesics.

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In addition to multiple pain mechanisms, we need to recognize that pain is not a monolithic single entity. There are different pain symptoms that may complicate a way to reflect these different mechanisms, and that if we use global pain scores, we may be missing some of the different mechanisms that operate in different conditions, so it is important for us to appreciate that there is spontaneous pain, pain that apparently arises without any peripherals or without any stimulus, and evoked pain, pain that occurs in response to some input.

Spontaneous pain itself may be divided between that that appears to derive from the skin, from the superficial structures of the body, and that which is deep. Indeed, there are differences between the pain that is continuous and that which is intermittent, and clinically, we certainly recognize that these are not the same.

Evoked pain, again there is enormous difference between pain that is evoked by thermal and mechanical stimuli, and it is important to differentiate pain that occurs in response to a

stimulus that normally would not be painful, what we call allodynia, and an exaggeration of the response to a noxious stimulus, that which we call hyperalgesia.

What I would like to argue is that each of these different categories reflects different activities in the nervous system and it is essential in performing clinical trials to try and capture as much of this information because it reflects some of the processing that generates the pain experience.

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To illustrate the points that I have made, I am going to look at the COX-2 selective or specific inhibitors and try and identify from our increased knowledge of the mechanisms that operate to produce pain, how there may be elements of pain that are sensitive to these classes of drugs and others that are not, and for that reason, why the discussion of whether it is appropriate to discuss global analgesics or even analgesics that are appropriate for all acute pain or all chronic pain needs to take into consideration some of these factors.

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So, to begin with, to come back to nociception, as I said before, this is the term that we use to describe the capacity of the nervous system to respond to particular intense stimuli, noxious stimuli, those stimuli which have the capacity to damage the body.

These stimuli are detected by highly specialized primary sensory neurons, the nociceptor neurons, which respond only to intense, and not to innocuous stimuli, and they feed into particular neurons within the central nervous system that transfers this information to that part of the cortex that eventually results in the sensation or the perception of pain.

This, if you like, is the "ouch" pain, the pain we feel in response to a pinprick or touching something that is too hot or too cold, and clearly, it has a major role as a protective mechanism, an early warning device, and that is something we need to appreciate because abolition of no nociception, while appropriate in some conditions, such as during surgical intervention, is not appropriate in the chronic setting.

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How does nociception generate? Well, if

we think back to 1992, we had almost no information on how noxious stimuli act on the nervous system to generate nociception, and in the last 10 years, the progress has been extraordinary. Only in the last few months has the receptor, the CRM1 receptor been cloned that converts cold stimuli into cold pain.

Heat pain is detected by a number of different receptors. About five years ago, the vanilloid receptor 1 was identified as being a heat transfuser, and only in the last month has another member of the vanilloid family, the TRPV3, the TRP channel V3 been identified.

So, we now know the individual ion channel receptors that respond to these noxious stimuli and produce generated potentials. There are also receptors that respond to chemicals released at the time of tissue damage, such as bradykinin, the B1 and B2 receptors, and we are at the point of understanding how intense mechanical stimuli are transfused into electrical activity.

Now, the point of going through all of these is that you will see there are no prostaglandin receptors, there is no COX-2 here, so that the process by means of which an intense thermal chemical or mechanical stimulus produces

nociception is COX-2 insensitive. No amount of COX-2 inhibitors given at anytime will affect the way we respond to pinprick or heat stimulus, so that COX-2 is not appropriate for that indication.

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If we look at the transfer of information from the primary sensory neuron to central neurons--and this is an attempt to cartoon the central terminal of nociceptors and their synaptic interaction with neurons in the spinal cord--we have identified the key transmitters that act to transfer this information.

There are both excitatory amino acids, such as glutamate and neuropeptides, such as substance P, and they act on a number of receptors on the postsynaptic neuron, both inotropic receptors and metabotropic receptors, and these can be modulated in different ways by a number of receptors which play a role in inhibitory mechanisms.

The GABAergic, particularly the GABA-A receptors, which control presynaptic release of transmitters and a number of other receptors, particularly the opiate receptors, which are expressed both pre- and post-synaptically, and can

reduce synaptic transmission.

So, opiate receptors and opioids, opiate receptor activation and opioids can certainly modify this transmission process and can reduce nociception, but again, you will see that there is no COX-2 or prostaglandins involved in this, and once again, nociception, both peripherally and centrally, is not COX-2 sensitive.

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That is essentially the conclusion made here.

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If we talk about COX-2 as being an analgesic, we need to take onboard that it is not a global analgesic, it does not reduce all pain in all circumstances, and it certainly will not reduce nociception, which is actually a desirable consequence of all chronic usage as I have indicated.

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We now move on to peripheral sensitization. This is the setting now where we have inflammation in the periphery. The peripheral terminal of nociceptors are exposed to inflammatory mediators, and this changes the peripheral terminal

in the way that this terminal can now be activated by stimuli that have a lower intensity, so that both stimuli that would normally not produce pain, and noxious stimuli produce a greater response, and this creates the situation where we have what is called primary hyperalgesia, which is abnormal pain sensitivity in the site of tissue damage, and one of the particular roles that peripheral sensitization has been shown to operate in is primary heat allodynia, the reduction in the heat threshold for producing pain.

Normally, we require stimulus of about 42 degrees for the conversion of a hot to a painful stimulus, but in the presence of inflammation, this can fall quite substantially.

What are the mechanisms involved in generating peripheral sensitization? Well, they are multiple, but the one that I want to highlight today is that as a result of the inflammatory response and the release of cytokines, particularly IL-1 beta and TNF-alpha, there is the induction of changes in cells surrounding the inflamed area of a number of enzymes and growth factors and chemokines, but the one here that I want to emphasize is COX-2, but if COX-2 and phospholipase

are induced at the site of peripheral inflammation, that results after action by specific tissue isomerases and the production of prostanoids, such as prostaglandin E2, which can then act on EP receptors, prostaglandin receptors that are expressed on the peripheral terminal of the primary nociceptor.

Prostaglandin, when it acts on the peripheral terminal, does not directly produce an activation of the peripheral terminal, it does not itself produce pain. What it does do is alter the excitability of the peripheral terminal, and we now know how that occurs. It is via activation of kinases that are present in the peripheral terminal that phosphorylate either transducive proteins, such as the vanilloid VR1 heat transducer, reducing its threshold of activation or it phosphorylates ion channels that are present in the peripheral terminal making the peripheral terminal hyperexcitable, so that less of a stimulus or less transducer action is required to activate the peripheral terminal.

I indicate there is a northern blot on the side showing that in normal skin, there is undetectable COX-2 levels, but within several hours

of peripheral inflammation, there is an enormous induction of this enzyme, and the point being that this particular pain is COX-2 sensitive. You cannot have COX-2 action if there is no target COX-2 expressed, but after peripheral information, it begins to be expressed, so this particular mechanism is COX-2 sensitive.

There are, in addition to prostanoids, other mechanisms that can drive peripheral sensitization, which means that COX-2 inhibitors may not completely eliminate this process. Bradykinin, amines may also produce these changes, this activation of kinases, which can phosphorylate some of these proteins.

Conceivably, drugs may be developed that can block these kinases and even their targets, such as the vanilloid receptor or the ion channels, and may actually totally abolish the changes that are produced by peripheral inflammation.

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I now want to move on to changes that can occur within the central nervous system, changes in the excitability of neurons which alter its responsiveness, and the situation here is that we now recognize that noxious stimuli produced by

irritants, tissue damage, inflammation, anything that can activate nociceptors can result in a use or activity-dependent plasticity within the central nervous system, altering the excitability of these central neurons, and this results in a situation whereby these neurons respond to normal inputs in an exaggerated or abnormal way.

This generates two broad changes that we can recognize in pain. One is secondary hyperalgesia, which is a change in sensitivity to pain outside of an area of tissue damage or inflammation.

Peripheral sensitization contributes to the pain sensitivity at the site of tissue damage, but central sensitization, this abnormal responsiveness of central neurons, contributes to the change in sensitivity that spreads into normal non-damaged or non-inflamed tissue outside the area of tissue damage.

One particular mechanism that we now recognize as being driven by central sensitization is tactile or brush-evoked allodynia. This is the pain that can occur by the activation of normal low-threshold mechanoreceptors that would be activated by lightly touching or brushing the skin.

After the induction of central sensitization, such stimuli can begin to produce pain, and this is a reflection of this mechanism.

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The reason why central sensitization produces changes in pain is it turns out that the pain projection neurons within the nervous system do not exclusively receive input from nociceptors, the high-threshold sensory fibers.

They receive, in addition, an input with weak synaptic input from low-threshold mechanoreceptors. This synaptic is normally too weak to drive the cells, so that activity generated by light touch, movement of a joint will not normally generate an output in the pain projection neurons, but if the excitability of the central neurons is increased, then, this normal input in normal, low-threshold mechanoreceptors can begin to drive these abnormally excitable central pain projection neurons and result in the recruitment of pain in response to this normal input.

This is the mechanism for brush-evoked mechanical allodynia.

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What actually produces the increase in

excitability of the central neurons and the specific details are not important for the purposes of this discussion, but just to say that it turns out there are two phases to the production of central sensitization.

There is an acute phase that occurs within seconds of the activity of nociceptors. If you activate nociceptors intensely, and this can be done by an irritant stimulus or heating the skin or tissue damage, that will result in the release of glutamate and beyond it, if there is enough glutamate released as a result of repetitive activity in nociceptors, that will induce activation of intracellular kinases, cyclic AMP-dependent protein kinase A, and calcium-sensitive protein kinase C, which will phosphorylate the receptors and ion channels on the postsynaptic membrane, altering their responsiveness.

So, there is an activity-dependent change in the excitability of the postsynaptic membrane due to the synaptic release. Again, you can see that while there are multiple players invoked in here, COX-2 is not a feature. So, this component of central sensitization, the acute component that is

switched on almost immediately by intense nociceptor activity is not COX-2 sensitive.

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However, it turns out that peripheral inflammation, in addition to inducing COX-2 in the site of tissue damage, as I have indicated, also induces COX-2 within the central nervous system, in the spinal cord, and this occurs after several hours.

The question is does this have any role in central sensitization.

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Well, there are two things to first recognize, is that the central induction of COX-2 occurs only in response to peripheral inflammation, and not in response to peripheral nerve damage, so again, we need to differentiate when we are looking at this mechanism the way it operates after tissue damage and inflammation is quite distinct from what happens after peripheral nerve injury.

It turns out that the late phase of central sensitization, that phase that occurs hours and days after tissue damage does involve COX-2, because COX-2 begins to be induced in neurons within the central nervous system, produces

prostaglandins which have multiple actions, increasing transmitter release, increasing the excitability of postsynaptic receptors, as well as blocking some inhibitory actions.

The net result is that the increase in excitability of central neurons acutely is not COX-2 sensitive, but that which occurs some hours after tissue damage begins to have a component that is COX-2 sensitive.

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So, the conclusions I would like to make from this is that there are COX-2 sensitive peripheral and central components of inflammatory pain, but not necessarily of the pain associated with peripheral nerve injury, that COX-2 inhibitors, as an example, can only act when their target is expressed. It needs to be induced. This takes a finite amount of time.

The cytokines IL-1 needs to produce, it needs to act on cells, which then switch on transcription factors, such NF kappa B, which then switch on the COX-2 gene, the messenger RNA has to be made, translated into protein, and this needs to be transported to the appropriate place in the cell.

This takes several hours, so that after peripheral inflammation, you only get a COX-2 sensitive component when the COX-2 is expressed and there.

There are also non-prostanoid contributors to inflammatory pain, and this may explain why COX-2 selective or sensitive inhibitors cannot produce a complete relief of pain. Other mechanisms continue to operate. So, that may contribute to the ceiling effect of these class of drugs.

I have already mentioned that peripheral nerve injury may not be present.

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So, I think we need to consider then what are the models that are appropriate for looking at the relationship between etiology and the symptom that we call pain.

Well, one possibility may be that different etiologies may act on the nervous system to produce different distinct mechanisms that may produce particular symptoms. If you need to treat the particular kind of pain associated with a particular etiology, you can target the individual mechanism.

Unfortunately, the reality as far as we can judge is more like this, that a single etiological factor can operate on the nervous system to operate multiple mechanisms. Peripheral sensitization and central sensitization are not independent, both can be switched on by peripheral inflammation.

Peripheral nerve injury can produce both ectopic excitability and central sensitization, and part of the challenge that we have is to try and identify the links between different etiological factors and the mechanisms they operate, as well as how the different mechanisms can change, produce the symptoms that the patient complains of.

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What I would like to try and suggest is that we need to differentiate between analgesic drugs, drugs where the implication is a global relief of pain, and drugs where there is a reduction of the abnormal sensitivity of the nervous system, and that this is a useful distinction.

I hope I have indicated to you that both the temporal and intensity characteristics of pain do not, by themselves, reflect mechanisms, that

they are different mechanisms that can operate to produce both acute and chronic pain, and that for this reason they may not, by themselves, be useful predictors of analgesic action.

I would like to argue that as we begin to understand more about pain mechanisms and the very particular mechanisms that individual drugs have, that it is this combination that is going to provide the most useful input for determining indication and efficacy.

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In order to make progress, we need to move away from using exclusively global pain scores as our outcome measures. We need outcome measures that are sensitive or specific to particular mechanisms, and that is a big challenge.

We need clinical trials that can validate mechanistic hypotheses and that are designed specifically to address the issue of which drugs acting on which mechanisms can alter the symptoms in particular groups of patients.

We need to consider labeling claims and the like to the action of drugs, with the interaction of the drugs with specific pain mechanisms, as well as the more traditional

approach, which has been empirical trials looking for efficacy.

My final conclusion is that I think--and this overlaps to some extent with the comments made by Jim Witter--are there going to be global analgesics. I think this is unlikely.

Pain has too many different mechanisms operating that it is very unlikely that a single drug is going to affect all of them and that the challenge we have is to try and optimize the way to detect which particular mechanisms an individual drug is operating to see the utility of blocking that mechanism for particular groups of trials and let that drive the labeling of the drugs.

Thank you.

DR. FIRESTEIN: Thank you very much for an excellent discussion.

Discussion Points #1 and 2

DR. FIRESTEIN: At this point, we can move into some of the discussion issues that were raised by Dr. Simon and the Agency. I believe that we were going to discuss Points No. 1 and 2. I will just read the first one and then open it to the group for comment.

1. A revised analgesic guidance may

include indications intended to inform labels for the management of acute versus chronic pain, rather than a general pain claim. Please comment on the clinical relevance of this distinction in terms of efficacy and safety.

if there is anybody who would like to get the ball rolling here? I suppose that then becomes the Chair's prerogative to comment and then have everybody disagree with me.

I think that the discussion that we have already had, defining the distinct mechanisms of pain, raised some of the issues about separate labels for acute versus chronic pain as opposed to a general pain claim versus a specific claim that is mechanism based.

I think in particular, one of the things that was discussed earlier was the question of whether chronic pain in some cases merely represents persistence of acute pain mechanisms, and how can one distinguish that in a chronic pain labeling is going to be quite difficult.

I don't know, Dr. Woolf, you might want to comment on that particular aspect.

DR. WOOLF: The point I was trying to make using the COX-2 inhibitors would be, to get down to

specifics, that although they may have an indication for chronic pain based on a number of replicate trials showing efficacy in chronic pain, the evidence indicating that there is no COX-2 induction of peripheral nerve injury, which may certainly produce chronic pain, would indicate that most patients with neuropathic pain may not respond to COX-2 inhibitors, so that an indication of chronic pain by itself is incomplete and may lead to inappropriate use of analgesics, which may not have efficacy in certain particular groups of patients.

So, the issue then is does chronic pain, by itself, have a meaning. I think we have just got to be a little cautious of that.

DR. FIRESTEIN: I guess on the other hand, it might at least bring us a little closer to reality as opposed to a more global pain indication, in other words, although there are clearly limitations between acute versus chronic pain, that is less problematic than trying to have a global pain indication that would cover all aspects of all pain indications.

DR. MAX: Gary, you have already in your question, you already indicated that this

distinction is mechanistically insufficient, because you said chronic back pain can have acute inflammation on top of it. I think it is clear from Clifford's talk that this does not do very much for us with mechanisms.

However, just from a practical clinical setting point of view, I think it is clear that when we talk about acute pain, we are talking about a specific clinical orientation of the patient. They have sudden bad pain and they are willing to do anything they can for a few days to handle it, and a little bit of impairment of work might be okay.

On the other hand, in chronic pain, we really need evidence from day-in, day-out living, not just the single dose trial, that the patient has got to be able to live with the analgesic regimen and the way of evaluating it is going to be much different.

So, I think the main argument for this division being important is the practical considerations, the clinical setting, are so much different that they really imply completely different clinical trial designs.

I mean once we take each, then, we can

bring in some of the mechanistic considerations that will be hard.

DR. FIRESTEIN: Dr. Brandt, did you have a comment?

DR. BRANDT: Yes. I think, Dr. Woolf, that was really a beautifully lucid and useful dissection of mechanisms. To bring it to osteoarthritis pain, I would like to ask whether it suggests a research approach.

Nonsteroidals for patients with osteoarthritis improve pain on average, on visual analog scales, 20, 25 percent. Some patients get terrific relief, some patients get worse, but on average, 20, 25 percent.

If you add acetaminophen to a nonsteroidal, you get a further increment, but there still is a significant amount of residual pain. Based on what you said, presumably, there is another mechanism that is driving it, how does one get at that, how does one study that to know what sort of drug might be useful or might be reasonably tested to get at that residual pain.

DR. WOOLF: Chronic osteoarthritis is a very interesting disease from a basic science point of view. The problem we have is that there are

very poor preclinical models that it is very difficult to test in the preclinical setting what the mechanisms are.

The fact that there is a response, even though modest, to standard NSAIDs when in most patients there is not ongoing inflammation, raises the issue of where is the COX-2 that presumably they are acting on, so I think the first research question is, is this a disease of the periphery in terms of COX-2 mechanisms or is the COX-2 induced in the central nervous system.

The fact that there is an additional contribution of acetaminophen would imply that that is likely to be the case.

The ceiling effect of NSAIDs is as you indicate, and the fact now with the second-generation COX-2's, where the doses can be pushed to a level where all conceivable COX-2 is likely to be inhibited certainly indicates that there is a residual mechanism that is not COX-2 sensitive.

What it is, is obviously the big challenge, and I could speculate, but I think this is where new drugs with new targets are coming onto the market. Some of them may be useful by

themselves, but I think in clinical practice, we know already that polypharmacy is a standard way in which patients are treated.

So, it is very likely that these new drugs, acting on different independent targets, will have a role, sometimes by themselves, but often in combination with existing therapy.

DR. FARRAR: Understanding that even in the realm of arthritis, it is very often difficult to identify in any given patient the primary cause for their discomfort, I wanted to ask Dr. Woolf whether, if we were able to identify a subset of arthritic patients who had, in fact, a very similar peripheral mechanism, whether that nice pathophysiology slide you showed with all the various mechanisms, whether all of those mechanisms would apply in every patient or whether, in fact, there would be within even a mechanistic approach, differences in the way that a particular patient responds to both the pain and the underlying treatment based on the fact that some may have a predominance of one kind of receptor over another or a predominance of one response over another.

DR. WOOLF: I think it is even more complicated than that. I think it is not only the

problem that individual patients within a particular group or clinical entity, a particular form of arthritis may have different mechanisms, but an individual patient over the evolution of their disease will almost certainly have different levels of contributions of the different mechanisms.

The challenge is how to identify them, and the fact, the comment that was made that some patients may respond extremely well to NSAIDs than others, I think that gives part of the clue. I think one of the tools that we are going to have to use are drugs to try and identify mechanisms.

Those patients who respond very well to COX-2 inhibitors, by definition, we are defining at least one component of their pain is COX-2 sensitive, whereas, those patients that don't, assuming the drug, the notions of bioavailability or PK, we can conclude that in those individual patients, there is not a COX-2 component.

So, I think we are going to have to use a combination of trying to link up symptoms with mechanisms, which is difficult, but not impossible, as well as the responsiveness of the patient to very specific forms of therapy.

DR. SHERRER: A question as it relates to chronic pain, because it was mentioned earlier by Dr. Witter, and it is certainly true clinically, that there are two types of chronic pain. There is the chronic persistent pain, and there is the chronic acute intermittent pain or intermittent pain at least.

Do those patients represent people with repetitive acute pain mechanisms even though it is one disease, such as the osteoarthritis patient who flares every few weeks or with a weather change or with activity, or, in fact, is that a different mechanism of chronic pain?

DR. WOOLF: I gave an example just to try and differentiate in the most global sense, but there will again be patients, such as those with trigeminal neuralgia, who will also have intermittent pain where the mechanism will be completely different from an OA patient with flare, so I hope I didn't give the impression that that represents two distinct mechanisms.

There may be again multiple mechanisms that operate between those two classes, but I think we are all aware of patients who have OA of the hip, when the hip is replaced, can do extremely

well with minimal recurrence of pain, where there are patients with peripheral neuropathic pain where the neuroma is removed, and they have a transient response and the pain comes back, so the point being that in some cases, removing the etiology, the cause, the hip, can actually remove the pain, whereas, in other patients, it appears as if the mechanisms have now been hard wired, if you like, and are resistant to, are no longer driven by the initial disease process.

DR. FIRESTEIN: Let's come back to one of the issues raised here, and that is whether or not there is utility to differentiating between acute versus chronic pain as compared with a general pain claim and, in particular, issues that relate not only to efficacy but safety.

One example of that would be for the selective COX-2 inhibitors where one dose might be approved for the treatment of acute pain and has had either a dosage creep that has then at least in the clinic led to use of some of these higher doses for chronic treatment, and some of the safety issues may not have been addressed in the clinical trials because of that.

Does anybody have a comment? Yes.

DR. ELASHOFF: What I wanted to ask is in the first day or so of pain, if you are labeling things for acute or for chronic, does one know in the beginning whether you ought to be using the ones labeled for acute, because you don't know whether it might turn out to be chronic or not, or might you have the knowledge to say you ought to be starting in with chronic, so would one always start with acute things and then switch, or does one potentially have the knowledge at the beginning that you might start out with chronic things.

So, it seems to me that the issue of the labeling has to also say, well, practically speaking, how would you know in any given situation which ones you are going to be using.

DR. FARRAR: I think we need to very carefully differentiate between how we use the medicine and what we are treating. The question you are asking really relates to whether the medicine is used over a long period of time or whether it is used over a short period of time.

I think the issue is not answerable from an acute or chronic perspective. If you take migraine headache, there are medicines that are used to prevent it, that are used regularly over a

long period of time, and then there are medicines that are used to treat it, which may be used over a very short period of time.

I think we need to differentiate between whether it is used over a long or short period, which can be done in a label, to say this drug can only be used for, it has only been shown to be safe for six weeks versus saying whether you are treating acute or chronic pain. I think those two are very different.

DR. CUSH: But aren't you just saying the same thing? I mean it is acute, a short period, and chronic if it's long term. We know that based on what the etiology of the pain is, the problem, whether it's postsurgical or dysmenorrhea or migraine, what our goals are as far as short term or long term.

But the terms of acute therapy and chronic therapy are useful. They dictate how we use these drugs. They dictate our expectations for these drugs. To go with a more general pain claim is too vague and not applicable to many patients that we use.

DR. FARRAR: But don't confuse acute treatment and chronic treatment with acute pain and

chronic pain. As was said here, you don't know when you start necessarily whether it is going to be a 2-day treatment or a 10-day treatment.

DR. CUSH: I think most physicians do know when they start out with managing pain what the goals are for pain management. Now, it is not to say that patients who start out with a migraine don't have a migraine that might be extending out beyond a few days, and acute therapies may not work, but I think that there are goals when you make a diagnosis and see a patient as far as whether it is going to be short-term therapy or long-term therapy.

DR. WOOD: I also found the last talk very interesting, but it seems to me the question that we need to debate is where the science is with this and whether the science is mature enough to actually make decisions on this.

I mean I would characterize this as being a bit like, say, leukemia. Leukemia is characterized by an increased white count, and clearly the management of leukemia depends on knowing a lot more than just that the number of white blood cells is increased.

You need to know the etiology, you need to

know the subset of patients, the subset this patient belongs to in order to define an appropriate therapy.

So, my question I think is the following - is the science mature enough or likely to become mature enough in the foreseeable future to divide patients into subsets based on the kind of divisions that Dr. Woolf described, and are we or will we be at a stage in the near future when we could make treatment decisions based on such subdivisions, or alternatively, is this solely at a stage where this should guide or direct drug development, and are you proposing this, not as a treatment decision paradigm, but one that would allow us to identify potential new targets for drug development, which--and this is important for this discussion--which we would then need to define in some way, a way in which we would approve the drug, because it is improbable that the approval will be based on some surrogate for the subsets you are talking about.

Does that make sense?

DR. WOOLF: Yes, I think so. The situation we are at currently has been based on the experience with both NSAIDs and opiates, and we now

have a sense of which patients are likely to respond, the kinds of outcome measures that are sensitive to that.

My concern is that the basic science is now revealing new targets which industry are developing new molecules, and the current models that the 1992 Guidelines reflect are not appropriate for that, that if we use these models, there may be heterogeneity of mechanisms in the patient groups that we study that will dilute the outcome measures to a point where it may look as if there is no efficacy globally, whereas, in fact, in the subgroups that do have the particular mechanisms, you would get very high efficacy, and that was a point that was raised by Dr. Fang earlier, that the responder rate may reflect the different incidences of mechanisms.

We are at a transition point where it is difficult to predict exactly how useful clinically the identification of mechanisms is likely to be, but I think equally, there is now enough evidence from the COX-2's where we are defining exactly how they produce the effects and efficacy to recognize that we can divide patients into COX-2 sensitive and COX-2 insensitive groups.

With that knowledge, we can identify some of the best ways to identify efficacy, as well as clinical utility.

DR. WOOD: But presumably, the COX-2 insensitive group includes all of the above, I mean everything that is not prostanoids mediated, so the heterogeneity in that group is probably at least as large as the heterogeneity in the total group. It is just lacking the prostanoids insensitive group.

So, how would you guide either therapeutic decisions on the basis of that, or alternatively, and more importantly I guess for this group, how would you guide the definition of patients to include in the trial that would demonstrate such efficacy, that is not just an exclusion?

DR. WOOD: Well, in terms of COX-2's, for example, that if the COX-2's have a label for acute pain, I think that would be too generous in the sense that procedural pain, pain associated with minor acute procedures that would generate nociceptor pain, would not be sensitive to COX-2's, and therefore, that would be an inappropriate usage.

Equally, there is minimal clinical data available, but if there were, I think it is likely

that postherpetic neuralgia and diabetic neuropathy are going to turn out not to be COX-2 sensitive, so that a chronic pain indication, a global chronic pain indication for COX-2's again would be inappropriate.

There would be some patients where that would not be likely to produce efficacy. The problem is there is still heterogeneity in the other groups, I accept that, and that is what makes it very difficult.

DR. FIRESTEIN: Dr. Ashburn, any comment?

DR. ASHBURN: One thing I wanted to point out is that we have been talking about several different definitions of acute versus chronic.

Dr. Hertz talked about that the 1992 advisory on analgesic drug approval discussed the concept of acute pain as being pain that existed very early on, had a fairly sudden onset and a short duration of action, and chronic pain was pain that had persisted for six weeks in a cancer patient, although I have cancer patients who would say that if it persists for two day, it is chronic, and chronic pain, for people who are not dying of cancer, has to last six months before it meets the definition.

Dr. Woolf gave what I believe is a more appropriate definition regarding the expected impact on the body and the expected reversibility of the pain.

On the other hand, some of the other speakers have really alluded to something which may be more important with regard to drug review, and that is, the duration of therapy, which is much more different, if the expected therapy is of short duration rather for long-term, chronic delivery.

I want to just point out that one issue has to do with regard to safety and durability of effect, which I think are very important factors that need to be investigated when a medication is being looked at for outcome. The other one has to do with defining different disease states with which to do studies. That had to with appropriate labeling with regard to dosing interval.

DR. FIRESTEIN: That actually begins to bring us towards the second question. We have a couple of other comments that people wanted to make, and then we will move on. But I think most people here seem to be in agreement that a general pain claim is rather vague and it is going to be difficult to approach from a mechanistic or even a

clinical perspective.

I think one of the things that we might want to consider, after hearing the elegant discussion on pain mechanisms, is in addition to acute and chronic, whether or not there might be a place for a third category, such as acute persistent, where patients that have acute mechanisms of pain, that are persistent and reversible, but need to take the medication for a prolonged period of time, might have even different criteria than other chronic indications.

Dr. Cush was next, then, we will get a couple of other comments, and then we will move on.

DR. CUSH: My comment is to Dr. Woolf. I think that many of us would like to see pain defined mechanistically in an effort to better control pain, maybe use complementary regimens to get more total control, if that were possible, a disease, such as osteoarthritis, but at this point, would you not say that we can maybe define mechanistically how certain drugs may work, and that might well go into some of the preclinical work that would go into maybe how a drug is defined as far as its mechanism of action, but we do not yet have the tools to define mechanistically how

these drugs work in clinical trial meaning that we don't have the tools for different diseases to say that this going to be a peripheral sensitizing drug or central, and whatnot.

DR. WOOLF: If we conduct clinical trials the way they have been at the moment, then, the answer is yes, because global pain scores are not going to identify mechanisms.

The big issue there is if we can gather more information, for example, I indicated the peripheral sensitization had a particular property, which is abnormal heat sensitivity in the site of inflammation, whereas, central sensitization was associated with tactile allodynia.

Now, if that inflammation were collected as part of secondary outcome measures, maybe we could get an indication whether new forms of therapy acted on those particular mechanisms in addition to whatever global effect they had on pain scores.

So, I think we need to move from seeing pain as this monolithic entity with a single expression, which is what the patient feels, to try and collect more data, in the same way that if we look at heart failure, we would make a number of

measurements - peripheral edema, hypertension, cardiac output, and treat those specifically.

I think we need to do the same with pain. The trouble is we are not exactly sure of the durability of these different components and their reflection to mechanisms, but I would argue global pain scores, by themselves, are too insensitive to pick up these individual mechanisms, and therefore, some drugs with some utility may be lost.

DR. FIRESTEIN: Two other quick comments. Dr. Davidoff, did you have a comment to make, and then Dr. Abramson, and then we will move to the second issue.

DR. DAVIDOFF: Yes, I would also like to add my appreciation for the discussion, which I think was very lucid. But in thinking about that and some of the other comments, it occurs to me that there might be another spectrum in which to make useful distinctions, perhaps even in terms of labeling.

That is, there appear to be certain clinical situations which are analogous to some of the, as you put it, preclinical models where the mechanism is relatively pure, and the models are chosen to be able to study a particular type of

pain.

There are others, mostly clinical situations, where it seems pretty obvious that the mechanisms are mixed, and the difficulty is trying to sort them out on some clinical basis whether it is from subtle clinical cues, maybe the development of testing that would allow you to identify the mechanism, or the therapeutic trial.

The power of a therapeutic trial, as Alastair has suggested, may actually reemerge as something very powerful, just the way the treatment of hypertension has evolved, so that it is not clear.

There are certain relatively pure forms of hypertension, like a pheo or primary aldosteronism, where the treatment is highly specific and narrowly defined, whereas, with most hypertension, it is much more difficult, and, in fact, patients are put on one drug and then a second drug, and a third drug, and nowadays, frequently four drugs, and the therapeutic response is really the way the diagnosis is made, if you were smart enough to know what each of those drugs was doing.

So, I wonder if it might be useful to add sort of a dimension of purity versus--how should I

say--pure versus mixed mechanisms as being one way to consider approaching the labeling.

DR. FIRESTEIN: Dr. Abramson.

DR. ABRAMSON: I think I had a related comment because it seems that the issue is less whether we should have an acute versus a chronic label, which I think we should because of the different clinical syndromes, but the issue is the heterogeneity of what we are going to be calling indications for clinical pain, and having to grapple with, it that too broad a concept.

I mean you are describing different pain mechanisms, and whether we will have a broad-based label is something I think is going to be difficult to grapple with.

I am a little concerned in that context, therefore, that to try and dichotomize mechanisms may be premature, in other words, many of these syndromes have to be mixed, as was just said, and some of the science is early and some of the observations don't take into account perhaps the kinetic changes over time.

So, I guess the question again for Dr. Woolf is how advanced are the preclinical models in terms of the expression of the different molecules

in the central and peripheral system and how might we think about, when we do clinical trials in chronic pain, differentiating these different mechanisms based on tissue expression of some of these molecules.

DR. WOOLF: I think your point is well made. We are certainly at a point where I think it is appropriate to discuss it and to try and build in our view of the way in which pain is generated to take into account mechanisms, but this is early.

This is a point where the kinetics I agree are poorly defined particularly in patients. Unfortunately, many of the changes, the expression of different molecules occur within the nervous system, so access in patients to tissue to actually determine them is extremely difficult.

The reliability of animal models for clinical diseases is a separate issue, which is obviously complicated, but I think we just need to try and include this as part of our operating definition of what pain is, and not just ignore the mechanism, particularly since we are at a point where we are about to get new forms of analgesics that have actions that are different NSAIDs and opiates, and as a consequence, may need different

outcome measures reflecting the action of a particular mechanism.

So, we are not there yet, but I think we are a point where, as new trials have been designed, we may need new approaches to them.

DR. FIRESTEIN: Actually, we have been migrating slowly towards Discussion Point 2, which specifically asks about mechanistic approaches versus clinical approaches, and maybe we can steer for the final five or 10 minutes of the session, the conversation towards the utility of those two approaches, whether scientifically we are at the point where we should be focusing strictly on mechanistic targets or whether or not the gold standard will be the patient's clinical syndrome.

DR. MAX: Let me follow up on Dr. Wood's question on where are we with the science of clinical analgesia. I think it is pretty primitive compared to the animal models because pain is a new enough field, with so few clinical investigators, mostly doing single center trials, that we haven't had the size of the clinical trials combined with the rigor to answer these questions.

I think we agree that we are mammals, and if Clifford can demonstrate all these different

mechanisms in rats, we can in people, and there are a number of examples in the laboratory with humans where we can do, say, a selective nerve block and knock out one kind of pain.

We expect that if we looked hard enough with the right tools and the large cohorts in many industry trials, we might find some interesting correlations to learn how to use the drugs better.

That is why better tools, if we could develop the equivalent of the arthritis trial groups' scales, we might find things, and I think Clifford's group is working on this, but we are quite primitive, like we have just done a trial with Hopkins looking at a crossover trial of placebo tricyclics and opioids in postherpetic neuralgia in 70 patients, and we find that one group responds to opioids, and an independent group responds to tricyclics, but to really prove that, you would need to replicate, you would need to give the patient back the same drug.

We haven't separated that from the possibility of random variation. So, I think the problem for this committee is to provide enough of an incentive for industry trials to try to look for mechanistically based advantages.

I don't think we can count on that coming out, but I think if we look a little harder, they are going to emerge.

DR. FIRESTEIN: Ken.

DR. BRANDT: I don't think that Question 2 is necessarily an either/or proposition. Coming to responsibilities of safety and efficacy and looking at drugs, if we come back to a way guidelines for management of OA both by the ACR and by ULAR, basically recommends starting with acetaminophen, and if that doesn't work, moving on basically on NSAIDs, and so on.

It occurs to me in thinking about Dr. Woolf's comments, we don't know how patients who fail acetaminophen respond to an NSAID. We assume that they are NSAID responsive and they will do better. We don't know that, and it might be useful in terms of this dissection, admittedly at a very crude level and admittedly with the caveat we don't have a clue how acetaminophen works, to get that sort of information in and see whether acetaminophen failures, how frequently they respond to NSAIDs and to agents that perform differently than COX-2 inhibition.

I think there is a place to start in this,

taking a disease that is understood to some extent.

DR. FIRESTEIN: But is it more useful to have a musculoskeletal approach or a mechanistic approach for these drugs, for instance, do we need to have separate rheumatoid arthritis and osteoarthritis indications?

In spite of what has been said, there actually is a fairly prominent inflammatory component, for instance, do we want inflammatory pain versus non-inflammatory pain, for instance, in musculoskeletal diseases.

DR. BRANDT: Well, I think the issue is that there are a number of origins of pain beyond inflammation. There is not any disagreement that OA has an inflammatory component, but, for example, I think that bone pain may be significant in osteoarthritis because of the alterations in bone hemodynamics.

That might evoke interest in a whole different class of drugs that would be relevant to OA pain, vaso-active types of medications, that it provides an opportunity by considering the pathophysiology of the disease, and I think you would agree there are differences between RA and OA in a broad sense, not just with regard to pain or

inflammation.

That might provide opportunities to explore different approaches to developing disease, perhaps specific analgesics.

DR. KATONA: My question is for Dr. Woolf. Do you have any idea on the developmental aspects of the different pain mechanisms? Just working along with children and adults, it is very obvious that in any inflammatory disease children, who have somewhat less pain, it is easier to be controlled, as well as acute situations don't get chronic as often as adults.

I am just wondering if you have ever looked at or whether you have any data on it.

DR. WOOLF: There certainly is a major interest in the developmental aspects of pain, and this is an area that I, myself, do not work on, but it appears as if the very early interventions in neonates may have consequences, long-term consequences that are quite different from a similar intervention in children and adults. That is one aspect that needs to be looked at, and then the separate aspect of the responsiveness of children themselves.

That raises the whole issue of what are

the mechanisms that operate or are responsible for the conversion of acute pain to chronic pain. We have heard discussion earlier of when you are giving an analgesic acutely, you may not know whether the patient is going to require that for a long time.

Our knowledge of why some patients go on to develop chronic pain, and others do not, is quite poor, and the difference between children and adults in that is certainly an important issue.

DR. FARRAR: I think the discussion point asks the question of whether a mechanistic approach or a clinical approach has a rationale, and I think that what we are hearing from Dr. Woolf and Dr. Brandt, and others, is that both of them are clearly applicable to the appropriate use of any medication.

It seems to me, though, that the point before the FDA is that we are not yet at the point to be able to mechanistically identify each and every patient that comes to see us. We are also, frankly, not even able to clinically identify at the beginning, the underlying clinical reason for a patient's disease process the first time they come to see us.

Understanding that the nature of the science of medicine is still very nascent, it is still very much at the beginning, that it is appropriate to consider the way in which a drug is labeled, to consider the way in which patients present and the way in which physicians will then treat them.

I am a neurologist. I would love to know what the underlying mechanism is of half the patients that I see who come to me for pain. In fact, I can't do that, even in patients with the same disease process, we cannot identify, necessarily identify their response.

In thinking about how a drug company therefore must perform tests to look and see whether the drug is working, I think it needs to focus on the way in which patients present, so that if we can develop a mechanism, Dr. Max was suggesting, a mechanism to be able to actually identify certain subgroups, then, it makes sense to perform trials in those particular subgroups.

Until that science catches up, we are left with treating patients with osteoarthritis. Treating patients with osteoarthritis means testing in osteoarthritis and understanding that the

underlying mechanisms may be very different in that same patient.

Where that leads to is again the issue of differentiating between the long-term use of a medication and treating a long-term process, because the two are very different, and I think we need to stick with the way in which medicines are likely to be used for the time being.

DR. FIRESTEIN: You have made some very cogent points. I think that while the science has progressed considerably with regard to mechanisms, in the end right now we are faced with patients that come into the clinic that may have multiple mechanisms for a particular clinical syndrome that we are going to be treating.

It is likely that at least for now, we need to focus on the clinical presentation for many patients.

Lee, I know that there is lots of people that had additional comments, but we need to move on. Are there any additional points that we need to address for this section?

DR. SIMON: Not right now except Dr. Goldkind has one more bit of information to add and a question to ask.

DR. GOLDKIND: Some of this has been addressed by Dr. Firestein. We need to remember that ultimately, the common pathway for approving an analgesic relates to the experience of pain, and so it may be worth discussing whether an indication that is mechanistic in development, but ultimately relates to a metric that is somewhat global, might not be the hybrid, you know, is allodynia associated with a condition, that could be a mechanistically driven indication, but it would still have to ultimately be reflected in the patient's experience.

I think we need to remember that the patient ultimately needs to be impacted in a meaningful way, and if it drives development to allow more detail and description in the label or some creativity in an indication, if there is an important benefit to be accrued.

DR. FIRESTEIN: There is probably general agreement with that.

I think we will end this session here. We will take a 10-minute break, so that we can get back on track. We will see you in a few minutes.

[Break.]

DR. FIRESTEIN: The next speaker is going

to be Dr. Lee Simon, the Division Director, and he is going to talk to us about chronic pain and the claim structure.

Claim Structure

Lee S. Simon, M.D.

DR. SIMON: Thank you, Dr. Firestein. I would like to thank again the members of the committee. I would like to take a moment and thank the Divisions of OTC and 170 Anesthetics and Critical Care, for lending us members of their committee to join with the Arthritis Advisory Committee given the fact that pain is such a broad and extraordinary large indication, it affects so many different syndromes and diseases, and much of what you can see our discussion relates to, do you do models or do you do diseases, and ultimately end, as Dr. Witter had suggested, how we do that depends on what we are trying to inform patients, are we trying to inform patients about the syndromes and diseases they suffer from and what kinds of drugs then interfere with them, or are we trying to think about ways that will do also driving new drug development.

I think much of these next several discussions that will be presented to you will have

a lot to do with that.

I would also like to just take a second to acknowledge my entire division that has spent weeks in putting these talks together. They have really done a spectacular job, and I would like to acknowledge the fact that this has been one of Dr. Jim Witter's pet projects over the years, even prior to my arrival, and is the culmination of a lot of work for Jim, and I think he has done a terrific job.

I would like to thank all of the guest speakers, some of which you have not yet heard, but given Dr. Woolf's superlative presentation, you can imagine the level of conversations we will have and presentations we will have.

In the context of chronic pain, let me remind you I am talking now about things that our division in 550, Analgesics, Anti-inflammatory and Ophthalmologic Drug Products, have grappled with and some of the advice that we have been providing some of you sponsors in the audience so far as it relates to the identity of chronic pain.

I think that it has been a really informative discussion to think about chronic pain, not just in the context of its chronicity, but also

in the context of how one uses a drug and how one then thinks about the safety, thus, how one would design a clinical trial to inform you about chronic pain.

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So, pain is always a subjective experience. Some people are quite stoic. My wife never seems to need any kind of anesthesia to get her teeth worked on, whereas, I have to put to sleep to get my teeth cleaned.

So, I think that the subjective experience really defines a lot of what we are trying to target here, and that is very important although Dr. Woolf has mentioned that the patient global response is not necessarily going to tell us much about mechanisms, but don't forget the subjective experience, it is important to know what the patient feels about the therapeutic response and whether they are adequately treated.

Everyone learns the meaning of pain through experiences usually related to following off your bike or falling around when you are trying to be a toddler and trying to reach that breakable thing on the chair or table above you.

As an unpleasant sensation, it becomes an

emotional experience over time, and it is clearly not only a physical stress, but an emotional stress, as well.

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I have had a really interesting opportunity. I was given the Merck Manual from 1899 as a gift when I participated as an author in the Merck Manual of 1999, so it allowed me to look back on pain and the therapy of pain in 1899 versus what we think about in 1999, and what the changes have been.

So, in one hundred years, as you heard from Dr. Woolf's talk, there has been clear progress in the field of understanding of pain, defining painful disease states and syndromes, along with delineating appropriate therapy.

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That is shown by this comparison between the original 1899 and now, 1999. So, this, in fact, is the original page from the index of indications from the 1899 Merck Manual, demonstrating pain and the definitions of pain.

You will notice that hepatalgia is a very important syndrome of pain in 1899, as was odontalgia, otalgia, ovarian neuralgia, very

specific definitions as you can see, clearly delineating the way we do today about different kinds of pain.

Furthermore, this is the entire list of available pain medications in 1899 that were suggested. Yellow are some of the things that have fallen out of favor, such as iodine or potassium cyanide, something that would not be readily available today for us to use.

On the other hand, the white actually demonstrate the drugs that were available in 1899, belladonna, chloral hydrate, codeine, morphine, menthol, some of which may be similar to the kinds of things we use today, like Arthritis-Eze, which is always advertised on the TV about the use of menthol, phenacetin, the parent product for acetaminophen, and sulpyrine was what they referred to as aspirin in those days. I actually didn't know that.

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So, looking now in 1999, this is just one of the pages of the index on pain. As you can see, we have clearly moved forward about categorizing pain in various different ways, both by some of the things you have heard about from Dr. Woolf, as well

as descriptors, such as after tooth extraction or bladder pain, abdominal pain, psychogenic pain, carpal tunnel syndrome, and this then actually goes on for three pages.

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What also interested us, the separate Analgesics Index, which, in fact, goes on for multiple pages, describes pain relief in terms of acute postoperative pain, or in cancer pain syndromes, or non-opiate drugs for pain, nonsteroidals, opiate drugs, so, in fact, it is really quite interesting how we have come along, where we have been, and where we are today.

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So, we have actually furthered our description of pain, but even 100 years ago, we fundamentally are using today the same fundamental drugs that they were using then - opioids, morphine and codeine, for example, nonsteroidals, as evidenced by salaparendi [ph], "effective aspirin," it was called in those days, forms of sedatives like chloral hydrate.

Well, we don't usually use chloral hydrate today for pain relief, but we certainly use other kinds of things that help people tolerate pain. We