don't really know how they work, for example, the tricyclic antidepressants, and then muscle relaxants.

So, I am not sure that we have come a long way in the analgesic development area. One of the reasons for that has to do with the issue of various descriptors of pain.

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This is an archaic way of actually bringing this about, and I thought that we would start here with this. Dr. Cush actually jokingly referred to this kind of archaic description prior to beginning this session.

Somatic pain, visceral pain, and neuropathic pain, not that neuropathic is archaic, but this issue of somatic and visceral are, so somatic pain - caused by the activation of pain receptors in either the cutaneous body surface or deeper tissues, such as musculoskeletal tissues, whereas, visceral pain, pain that is caused by activation of pain receptors, gee, a really similar kind of description, not exactly the way Dr. Woolf would have necessarily described the various different effector agents of somatic or visceral pain.

So, pain receptors from infiltration, compression, extension or stretching of the thoracic, abdominal, or pelvic viscera, such as chest, stomach, and pelvic areas.

What has actually survived this archaic descriptors is the neuropathic pain - caused by injury to the nervous system either as a result of a tumor compressing nerves or the spinal cord, or cancer actually infiltrating the nerves or spinal cord, but unfortunately, this now definition removes or leaves out the issue of inflammation to the nerve root as part of the causal relationship of neuropathic pain.

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Then, we move to something we have already talked about, not just the sense of where it is in the body, but, in fact, the descriptors of how severe it is, so mild, moderate to severe. They are very useful as descriptions. Patients understand severe pain versus mild pain, but to any one patient, that might be very different, so for me, I think walking into the dentist office is severe pain without even having them do anything.

So, it does not provide any rigor. Perhaps these should be used to modify the

definitions of acute and chronic pain indications, which perhaps might allow patients to understand more about how to use, but what measure do you apply for mild, moderate, severe, and ultimately, that measure, either defined by the sponsor or by the agency in evaluating that measure, ultimately, it is the bias of the agency, investigators, and sponsors to suggest which is really which, which is mild, which is severe, which then brings us up to acute versus chronic pain.

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I would like to remind you when we think about this, I think the discussion that was ensuing right before we took the break was really a critical one. It is both a temporal sequence, as well as the idea that the mechanisms are separate. It shouldn't necessarily mean that we are defining them absolutely. This is an area that is iterative, it is still in development.

We don't have a clue about all the aspects, as you have already heard, and, in fact, I expect that in 10 years from now, we will know a lot more than we do today.

So, acute pain - short-lasting, so temporal component, manifesting in objective ways,

perhaps that is mechanistic. It can be easily described and observed.

It may be clinically associated with diaphoresis and tachycardia, so there are clinical events that take place associated with the transient events, the transient stimulus that leads to the acute pain.

Maybe only lasting several days, increasing intensity over time, which might lead to this issue of that bridge between acute and chronic, the subacute pain. It can occur intermittently, episodic or intermittent pain. Dr. Sherrer referred to an OA flare superimposed on top of a more chronic event.

Usually related to a discrete event for onset, such as postoperative, post-trauma, fracture.

And then there is chronic pain - long-term, typically defined if it lasts for greater than three months, in the context of cancer pain, perhaps less based on survival issues. More subjective and not as easily clinically characterized as acute pain, and has a more psychological overlay.

I don't mean to suggest that we are

incapable of understanding and identifying chronic pain, but tachycardia and diaphoresis is not necessarily associated with the onset of chronic pain. This kind of pain usually affects a person's life, changing personality, and their ability to function, as well as their overall lifestyle.

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That brings us to a discussion that Dr. Firestein led just before - what about the general descriptor of pain, why can't we just label these things for pain and let the marketplace decide, why can't we just say it works in this kind of pain, and you could try it in something else, and if it doesn't work, you try something else.

That might be helpful and useful, but it is not particularly informative to patients, particularly with what we know today. The general pain definition has been broadly used in the past, however, acute and chronic indications use different models, may be mechanistically different, and have different safety issues.

Furthermore, the psychological component clearly separates acute pain from chronic pain, and that may have very important implications for therapeutic intervention, patient response, and

patient safety claims.

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Unfortunately, one of the major proponents of this kind of meeting was not able to make it today, and I wanted to allow Dr. Lipman to seem like he is actually in the audience by bringing up some of the things that he has referred to in the past, one of which is this particular statement from a paper in Cancer Nursing, which is that chronic pain has a psycho-social component that must be dealt with before depression becomes a part of the clinical picture. Chronic pain should be recognized as a multi-factorial disease state. So it is a state that is responding to something, but nonetheless, may be an independent disease state requiring intervention at many levels.

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This diagram actually reflects these many levels and demonstrates the interaction that over time basically, whatever the pathologic process is, associated with the interaction with physical factors, leads to anxiety, depression, and psychological factors overlying each of these events, so that in the right circumstance and in the right patient, there could be issues of

isolation and loneliness, totally informing the patient leading to increasing anxiety and depression, the issues of hostility, why me, why is this happening to me, why can't I deal with this, and then the issues of social factors, which lead to the increasing loneliness and anger associated with this increasing isolation, thus suggesting a time period that we are liable for being able to intervene, to be able to allow this cascade of events perhaps not to progress.

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So, in thinking about trial design from the regulatory point of view, we have to think about again how Dr. Witter suggested, what are the issues regarding how to inform patients about their use of these particular therapeutic interventions.

So, look for trial designs that will allow us to see the result of how to translate the use to the patient, so as Dr. Hertz suggested before, we are becoming much more interested in disease states to be studied than models to be studied.

At the time, we didn't have a lot of understanding of the diseases. It seemed reasonable to try to look at models, but is alveolar bone pain in dental extraction the same as

bunionectomy, is dysmenorrhea, which actually has a clear mechanism of understanding of why there is cramping and abdominal discomfort, is that actually extrapolatable in a general way to other forms of pain.

So, some of the models that we were looking at are disease states that we have been looking at, have been osteoarthritis, chronic low back pain, which has been a big debate, some of which we will be informed in a little bit by Dr. Borenstein, fibromyalgia, an area of great and intense investigation, which has some very interesting aspects to the psychological overlay of how people deal with their pain, and perhaps genetics, about who selects out the individual response to an inciting event, and then who goes on to develop a chronic pain syndrome without further inciting episodes.

Neuropathic pain, and there are many of those, I just selected out two - diabetic neuropathy and amyotrophy, cancer pain and the old issues associated with that, that are quite unique. Temporomandibular joint pain, peripheral vascular disease perhaps, and then not only the disease states or models, but what about mechanistic

approaches.

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I am going to present three different possibilities for your consideration. I almost feel like Rod Serling in creating the Twilight Zone. These are all just for your consideration. We would like to throw out the possibility that we want to engender drug development.

We think this might be a good way to go, but now that I am on the light side rather than the other side, perhaps I don't have the right perspective that other people have about what is necessary, so we have to think about this together as whether or not these are the right ways to do things.

So, possible indications of one disease or model, one could even add in mechanism perhaps, an example, signs and symptoms of osteoarthritis. Not everybody knows that OA is osteoarthritis but us rheumatologists do. So, an example, signs and symptoms of OA, two replicate randomized and controlled trials, three co-primary outcomes in which each must win, so it would be pain, function, and a patient-determined global. And why would we want that latter one is again it is important for

us to know how the patient feels, not unimportant in labeling and allowing other patients to know what that means. There yet may be other measures that become important as we will talk about in a second.

There needs to be superiority to placebo or perhaps superiority to an active comparator. There could even be discussions, although it is not on this slide, about non-inferiority to an active comparator, but, in fact, that would have to be defined based on some issues as shown in the appended paper from Ellenberg and Temple about placebo responses and things like that.

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There is also the possibility of thinking about a whole organ system indication, such as musculoskeletal disease, and then one might think about, for example, improvement in the pain of musculoskeletal disease.

Three models of diseases, though, might be required to achieve this, all within the rubric of musculoskeletal disease, so low back pain perhaps in association with studies in osteoarthritis, and then perhaps also in fibromyalgia, all of which affect the musculoskeletal system, we believe, and

perhaps inform us somewhat about the use in a general way in musculoskeletal disease.

You will need two replicate randomized, controlled trials for each model or disease state. There need to be three co-primary outcomes, each of which have to be won on, of pain, function, and patient-determined global, and it could be superiority to placebo or superiority to active comparator, or maybe in the right circumstance non-inferiority that we could discuss.

The important aspect of this would be that the label would reflect, not just the idea of musculoskeletal disease, but reflect the approval of all the disease or models that had been studied, so therefore, you would get the approval for musculoskeletal disease in osteoarthritis and fibromyalgia and chronic low back pain, which would be actually in the label, as well as in the Clinical Studies Section, to inform people about the responses.

Furthermore, we would be even interested in discussing the issue of, well, gee, in fibromyalgia, maybe wind-up, the concept of wind-up pain is really critical, and perhaps, in fact, if you could interfere with that, in drugs that are

quite unique, that have nothing to do with what we have thought about pain before, such as an NMDA inhibitor, perhaps that might be the right way to go and achieve that for fibromyalgia.

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Then, the big discussion point that a lot of people have heard before and we have informed people about is the idea of a general chronic pain indication. Now, this seems to be quite a high bar, however, just think about how high a bar it reflects, meaning it could be suggesting that drugs could be used in any form of chronic pain.

Now, this leads us to a discussion of lumping and splitting, and some of the discussion we have had to date would suggest that it is going to be impossible as we learn more mechanisms to actually get a drug that would be appropriate for chronic pain totally, and that may well be true.

Thus, I would take you through this argument, suggesting that replicate trials in each model should be in disparate diseases, so you would have to study one aspect of musculoskeletal disease, one aspect of cancer pain, and perhaps one aspect of neuropathic pain, and that product, whatever that product might be, would have to win

in all three areas.

However, this is not to limit the possible areas. It may be that you could figure out something else besides neuropathic pain to study and thus get the same rubric - must measure pain, patient global, and some functional outcomes are the co-primaries, and again win, must be superior to placebo in all three and superior to the active comparator, and again, I point out that the label reflect two issues.

One would be the approval for the broad category, limited specifically by safety considerations, and the label will also, based on the data accumulated to achieve this, would demonstrate that the therapy is approved for the indication of chronic pain, but also the three diseases or models or mechanisms that had been studied, so therefore, it is kind of four things.

You get all three areas, perhaps other areas that you were also studied in, so if you did musculoskeletal disease into two different areas of osteoarthritis and chronic low back pain, they also would be referenced in the label and in the Clinical Trial section as thought appropriate for patients information and clinician information.

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Yet, there is still yet another approach, which we certainly want to encourage, although we are not entirely sure how to go about doing it, I don't know if you are, is the mechanistic approach. We don't yet know how to do it, we don't really know the models, but possible examples, as Dr. Witter alluded to, perhaps alteration of wind-up by inhibition of NUDA receptors in fibromyalgia, alteration of brain plasticity or neuroplasticity, alteration of early markers that might predict specific and verified clinical outcomes, thus giving a broad opportunity to really drive the science and improve drug development.

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All of this has to be remembered in the context that we, at the Agency, have to label things in the context of benefit to risk. So, as this cartoon suggests, as this unfortunate person sitting at this particular cafe selecting out which food to choose, and seeing the risks and benefits that are listed up on each one, it would not be dissimilar from a physician, patient, or clinician choosing particular drugs to choose based on their benefits to risk, as listed within documentation

that had been accumulated in trial development.

Thank you very much.

DR. FIRESTEIN: Thank you, Lee.

Discussion Points #3 and 4

DR. FIRESTEIN: At this point, we have been asked to discuss Points 3 and 4 here. Yes?

DR. MAX: I would like to comment to Lee. As I have said to you before, I really like one thing you said, and I am really profoundly worried and I really hate another thing you said.

What I really like is that your primary goal is to advance the science by encouraging many clinical trials in many diseases, and I have written a review article in Anesthesiology last July with Clifford, where we conclude that the best way to learn about mechanisms in human is from clinical trials in many diseases, and your approach does that.

The one thing--and I think it is a detail that I am very concerned with--is your stipulation that each trial needs to demonstrate, at the same time, a win for not only pain, pain scores over placebo, but in addition, a global outcome, global patient preference, and quality of life.

I would argue that if you look at large

databases of opioid trials and malignant and nonmalignant pain, as my colleagues in the Anesthetic Division have, and in my experience looked at chronic neuropathic pain and chronic back pain in other trials, it is unusual that one shows all three at once, and maybe we are behind you in OA, and I am afraid if you tell industry that you need to have a win in all three for each positive trial, that it's a why study pain, let's give that up, it's an impossible thing to meet.

I would propose the alternative, that you show pain is reduced more than a placebo by statistically significant outcomes, and at least you show evidence that you are not intoxicating the patient, there is no deterioration in the global or in the patient preference, and perhaps as an additional tier, you can get additional claim to give the incentive to develop better quality of life. That's my counterproposal.

DR. SIMON: I would just like to point out that, and I am delighted that I have stimulated this kind of discussion, that the quality of life measures are not necessarily the same thing as function, and what we are relating to are functional measures, not necessarily requiring the

bar of achieving an improvement in quality of life, although that is very important to us and certainly would be a secondary outcome that we would be looking for.

It is unfortunate that a lot of the definitions of health-related quality of life measures have been assumed to be measures of function. It is not necessarily clear that all are measures of function, and I am not yet sure that we have all the measures that we need to achieve this particular proposal.

It may well be that measures of function yet need to be developed in cancer, for example, that will allow us, to inform us in the relative short term of study, that patients with cancer whose pain is improved would benefit from function, as well.

This is a suggestion of not just the development of new drugs, but new outcome measures that is critical, and I think Dr. Strand will be discussing some of the issues about the tiered nature of how to look at that question.

DR. FIRESTEIN: Dr. Strand.

DR. STRAND: I just wanted to comment back to you, Mitch, that, in fact, we know from

certainly musculoskeletal diseases, OA and RA, that when you improve pain, and even if that is the most that you seem to improve in terms of the disease, such as the COX-2's in, say, rheumatoid arthritis, you are still getting responder analyses, you are still showing improvement in physical function, and improvement in health-related quality of life.

So, in fact, these domains are affected very significantly by pain and they are improved by pain, so I think that perhaps the bar is not as high as you might think.

Obviously, we have to look at it in terms of what disease states or what mechanisms of pain we are trying to treat, but it goes to show that with the multiple ways pain affects people in their day-to-day lives, if we are improving that, we should see it in these other aspects.

DR. FIRESTEIN: I guess the other issue is whether pain and these other outcome variables, especially quality of life, are independent. I think we have had a lot of these discussions with regard to rheumatoid arthritis and osteoarthritis where quality of life is a dependent variable on pain, as well as other aspects of joint destruction.

So, it is not clear to me that you gain a lot from a measure of quality of life if you don't get a win because of statistical vagaries or an inaccurate instrument for measuring that when the patient is subjectively better based on other criteria for pain.

Yes, and then Dr. Katz.

DR. ELASHOFF: Yes, the whole issue of exactly what the correlation is between these measurements across patients or across studies is an empirical one. I suspect that they are never completely independent, but that the correlation in some cases might be low and in other cases it might be high.

I think one needs to think conceptually of what one might expect in any given situation and why you might expect them to be less correlated or more correlated, but this is an empirical question on which a lot of light could be thrown by proper analysis of older studies.

Typically, there isn't enough in-depth analysis of exactly what the relationships are among various outcome measurements, and I would like to encourage that not only new studies be asked to really look in detail at the relationships

between these outcome variables, but that older studies could be re-analyzed to address that question.

DR. KATZ: I would like to caution against a "one size fits all" strategy with regard to what domains one might require to say that a trial is successful or not successful, and I would also like to caution against an overly enthusiastic generalization from the rheumatic diseases to other types of pain in that regard.

For example, it is clear that if somebody is on their death bed with cancer pain, you know, one's obligation is to relieve pain and its associated suffering, and the opioids are a miraculous and time-proven strategy for that.

To then require that that patient get out of bed and walk down the block, or do some other, you know, or improve functionally in some way would be a big mistake and would prevent us from really achieving our primary goals in that situation.

Certainly, one could design a functional measure heavily weighted towards pain that might show function, but that is, you know, just a remeasurement trick that doesn't really accomplish anything I don't think.

Similarly, in the patient, a 75-year-old with postherpetic neuralgia, with a 4 out of 10 pain, they might be pretty much doing what they need to do every day anyway, and that doesn't meant that relieving their pain is not an accomplishment even though it would be very tricky to design a functional or quality of life measure that would show dramatic improvement.

Lastly, you have got some really bad power calculation issues in terms of powering a trial to improve an SF-36 or something like that. It really sets a very high financial and feasibility threshold when, in many cases, relieving pain is really the primary goal.

Although in osteoarthritis, I can certainly accept that function is an intrinsic part of what we are trying to improve there, and in that context, it may make more sense, so I think we need to think carefully about each individual situation.

DR. FIRESTEIN: Dr. Callahan and then Dr. Cush.

DR. CALLAHAN: First, I would like to agree probably in musculoskeletal diseases, they are very different, but I do agree with Dr. Strand in terms of pain and function are highly

correlated.

My question was for Lee. When you say pain based on our discussions this morning, are you talking about a global pain or talking about various types of pain to get a global pain, as well as specific pain that would get at more of what was presented by Dr. Woolf?

DR. SIMON: Dr. Firestein, can I answer that?

DR. FIRESTEIN: Of course.

DR. SIMON: Thank you.

DR. FIRESTEIN: The Chair appreciates your request.

DR. SIMON: I learn from previous experience.

I think that your question really relates to the lack of development of the area. If this was five years hence, and Dr. Woolf's scenario was translated to a specific new receptor inhibitor, we would likely be thinking exactly in the terms that you have just said.

Our problem is, is that we are not yet there. I could envision three different receptor inhibitors demonstrating improvement and perhaps even getting a moniker chronic pain indication

depending on whether or not they are broad enough to warrant that, again going back to the lumping and splitting concept.

Yes, I believe in the splitting concept because I think that, and I think much of our division does, many in our division do, because I think the reasons for that are very logical and disease-specific and mechanistic understood.

For example, in acute pain, I can't imagine that a drug that necessarily works in dysmenorrhea will necessarily work in bunionectomy, and just because it works in dysmenorrhea and is a good model to study for that particular event, and it tells you something about one day of use, doesn't mean it is translatable to other forms of pain, but I think we are limited.

We don't have all of that information yet. I would like to believe that what I have proposed or what we have proposed may actually lead us in the way to develop more, not less.

DR. CUSH: My comments are directed at Lee and Jim, that I think given the comments of Dr. Max and Dr. Katz, I think that to consider a pain indication is reasonable and then to define that, that the indication here is pain, but there is also

improvement, not only in pain, but in quality of life or function or in a patient global, that could be in the indication as determined by the research that is done, might be very useful to users and to patients and whatnot.

To get to your suggestions regarding indications, I like the idea of disease-specific, organ-specific, and then global indications, I think that that sets sort of sequentially more difficult tasks, but greater implications to the populace, and I think that the design you laid out would be very useful.

DR. FIRESTEIN: Dr. Abramson and then Dr. Ashburn.

DR. ABRAMSON: Lee, I would just like address the splitters versus lumpers question and make a case for splitting.

Even in the realm, the domain of musculoskeletal disease, because fibromyalgia, OA, and low back pain are obviously going at different mechanisms perhaps, and I think we are at a moment now where we can hypothesis test some of the mechanistic concepts, and we can do it using clinical studies.

I think if we look at fibromyalgia

differently, if we lump them, we may lose the opportunity to looking at different mechanistic-based pain pathways. So, I would argue for splitting largely as a way to do clinical trials to test these different potential mechanisms neatly and cleanly.

DR. ASHBURN: I found your presentation to be quite interesting and I think that many of your aspects were starting to be well thought out, but I have the same sort of love-hate relationship that Dr. Max presented before, because one of the things that you alluded to even when you were talking about your experience in the dentist and your wife's experience in dentists, is that pain is many things.

Pain is not purely nociception, which many physicians think of it, but rather, pain is a global area, and it is best treated using a bio-psycho-social model of care including interdisciplinary care of which medical management is only one part of the care.

When one is talking about taking care of patients with complex disease, even I think of headache as complex, maybe my neurology colleagues don't think of it, but those patients are fairly

complex. Medical management is only one part.

The NIH Consensus Conference was done almost a decade ago now, presented that self-management techniques were equally efficacious to the medical interventions that we frequently focus on.

So, one of the issues is that setting study and outcome measurements in those patients is a good start, but is fairly difficult to do. There are disease-specific measures of health that Dr. Carr may talk about that are under development with regard to the care of individuals who have complex pain problems, but they are in their infancy.

They frequently look at function, they look at physical function, as well as mental function, and they usually have several different scores enveloped into one area, and then the question would be, drilling down, is improvement in one functional score adequate, is improvement in many adequate, does it matter.

Those are the sort of issues that make me nervous, and the concern that I have is, is that while it is an excellent idea to integrate measurement of outcomes amongst a wide variety of fields as a requirement to looking at new

medications, requiring that positive benefit be shown may be a barrier to care and may actually decrease interest in the development of new medications for the treatment of these patients.

DR. FARRAR: I have to say that I really enjoy coming to these meetings because I get to sit in a room with a group of real experts and hear them disagree vehemently about things that we are all talking about, and yet with the same common goal, which is to strive to make patients' lives better, which is ultimately what medicine is about.

I think, in part, I won't comment on what I loved and hated about Dr. Simon's presentation, but one of the things that he said that certainly is applicable to this, is that things are going to change and that we are not targeted today or we are not charged today with coming up with the final and ultimate answer, that we are charged with coming up with what makes the most sense for right now.

It made me think about the fact that we really have to be honest with ourselves. If we had a drug that was absolutely spectacular in the treatment of pain, in the way that penicillin was with pneumococcal pneumonia, you wouldn't need a randomized trial and you could use any measure you

care to use, and you would come up with a positive result.

What comes to mind in pain management is hip replacement in an old patient who has a broken hip that is amenable to that treatment. I mean any way you look at that, the patient is better. The patient's pain is better, they can walk again, they can get out of bed. Any measure you care to use would work.

The unfortunate part is that in medications, we are not yet at that step. It seems to me, therefore, that what we are charged with really is providing enough information to the people who are going to be using these medications to allow them to make reasonable choices about how they treat their patients.

I agree that, you know, the clinician on the front line is faced with a whole bunch of different choices, and if we can figure out the mechanism and figure out a test that will give them the mechanism, then, by all means, a mechanistic approach makes sense.

If can figure out whether we know this patient is going to develop an allergic reaction and this one is not, then, we should choose

obviously only the group that has the allergic reaction.

It occurs to me that we are not there yet, and that really, in many ways, what the label needs to reflect--and I keep coming back to the label because ultimately, that is what gets out to the public and then obviously clinical trials on top of that, but what the label needs to reflect is what is it that we know about this drug, do we know that it is safe given in three doses, do we know that it is safe given in 1,000 or in 500 milligrams, do we know that it is safe in terms of kids or adults or pregnant and not.

In terms of efficacy, do we know that it works when given in a single dose--that is important--do we know that it works when it is given over a long-term period of time.

With that kind of information in hand, I think it is possible to practice medicine, and that is really what we are targeted at doing today. Clearly, one size does not fit all, and every drug is going to have a different set of underlying things that we need to know about it.

That makes the job very, very complicated, which is clearly indicated by the amount of

disagreement that we have, but I think we need to focus on that.

DR. FIRESTEIN: Thank you, although I don't think the sham surgery for hip replacement protocol has been completed yet.

DR. STRAND: I just wanted to say that neither should we be trying to shove responder analyses based on other diseases into the pain field, and the fact that RA and OA have actually been addressed very differently from that point of view, but that we should really be thinking about these things as domains, domains of physical function or function period domains of health-related quality of life, and not pick the instrument.

We have lots of disease-specific instruments for various kinds of diseases, we have ones for cancer pain, et cetera, so that we don't have to shove the idea into a situation where it is not clinically appropriate.

DR. McLESKEY: Well, Lee, you certainly stimulated the discussion. As the industry representative, I would probably be negligent in my duty here if I didn't have at least some response at this stage.

I would like to echo Dr. Farrar's comment of a minute ago that obviously our entire goal for being here, your agency, and the various roles of the folks in this room is to advance the practice of medicine, to advance the options available to treat patients.

I hope we keep that foremost in our minds as we discuss all of these various issues, what will optimize that result, what will optimize the advance of the practice of medicine and how can we safely achieve that goal with advances in the medications available to our patient public.

The pushback that I have heard you receive already or your comments receive already from a couple of the members of the committee on this side of the table specifically, I think probably is representative of the novel concept that you have approached, the innovative concept that you have approached, and expected kind of a result from that, understanding our current knowledge base of disease models, and so forth, and how to measure accurately the effectiveness, and so forth, of various medications.

The concept that you mentioned especially for a general claim of three disease states and

having to hit on all three of the aspects of pain, function, and global, to me seems like a pretty high bar, and I wonder if the industry colleagues of mine in the room would not feel similarly, and yet, on the other hand, we don't want to act like antagonists and pull back and push back and oppose advances as the advances in the understanding of the mechanisms of pain have been discussed earlier today.

So, I would just suggest that we don't want to make the hurdle so high that, in fact, it will stifle innovation and move exactly in the direction we don't want to go. We want to stimulate innovation and advance and move forward.

So, again, I hope I am not coming across as somebody who is antagonistic to advance, I am not, but I think to accurately represent industry, we would like in the future to work closely with the regulatory authorities and with the academicians, and so forth, to come up with some kind of a compromise approach that is reasonable, that provides a hurdle that we think we can get over and accomplish the eventual mission of pushing medicine forward.

DR. FIRESTEIN: On the other hand, maybe

the bar for a global pain indication needs to be high because a drug that really is or a therapeutic that really is appropriate for all pain indications, as a global pain indication would suggest, is not really practical at least with the current state of knowledge.

There are so many mechanisms of pain, it is actually unlikely that we would find something that is effective for wind-up pain and fibromyalgia and osteoarthritis and cancer pain, and the question is whether or not, under those circumstances, the graded approach that has been suggested, in particular a disease-oriented approach followed by an organ-oriented approach, followed by a global pain indication is reasonable because the final Holy Grail of global pain is, in practical terms, not really approachable based on the science that we have heard today and has been written about over the past several years.

DR. McLESKEY: Perhaps so, but on the other hand, the comments that I have heard from Dr. Farrar and others indicate that maybe we are not quite there yet, and are we trying to run a little bit too soon before we have perfected the issue of walking.

But, nevertheless, as you have said, that in order to achieve a global claim, which would obviously be attractive to industry, and I would argue would be attractive to clinicians to some degree, as well, to offer them flexibility, and so forth, if we are to hit on three separate indications or diseases and to perform those indications in replicate, and on each of those hit on the three issues of pain, function, and global, that implies to me that the sponsor would have to perform a substantial number of pivotal trials in order to achieve that mission, which again makes the hurdle extremely high.

DR. BRANDT: Just a question for clarification based on what you just said, Gary. You referred to global pain. My understanding of a patient global, for example, is a little different from that, and one of the problems is there are many, many, many globals, it depends on how you ask the question.

For example, taking all things into account, how is your arthritis or how is your disease doing, which takes into account side effects, it takes into account other joints than the index joint and so on.

Perhaps Lee could clarify what he meant by his global.

DR. FIRESTEIN: Well, my understanding is that global means all pain, all indications.

DR. SIMON: Actually, let's be very clear. A patients global response is very different than a global indication, and so we would ask for patients to tell us how they feel, as Dr. Brandt has suggested, but Dr. Firestein, I think--I don't mean to put words in your mouth although I am delighted about what you said--was referring to the concept that this high bar would likely stimulate further development because, in fact, it would allow us to look at a therapeutic that would be active in very different disease states, thus, a global chronic pain indication. A very different use of the "global."

DR. WOOLF: I think this issue has implications for the preclinical development of analgesics which we haven't really spoken about, but the information that can be derived in terms of global action across a matrix of pain models is essential.

I think that as the development plan for any given analgesic is entered into, we need to

have as good an evidence as possible of the action of the particular drug, its specific action in terms of which targets it is interacting and its relative efficacy in a broad range of different models, models that are maybe more sophisticated than some of the ones that are being currently used.

DR. MAX: Let me put forth what I hear is the consensus around the table and see if it really is. I think we may be suggesting to you that there is no objection to having a general pain claim that requires two studies in each of three different disease categories.

We could learn a lot from all the different studies that will come in, and I just hear some objection to making the lowest level general pain claim have each of the six trials get all three endpoints, and the counterproposal is that general pain can be six trials, 3 times 2, each getting pain, is reduced significantly, but to get statistically significant global patients and function would be incentivized by a higher level reward, just like the rheumatoid arthritis claims do that, and I think I agree with Vibeke and others that it is important to have an incentive to

develop better measures because there are real issue, should we be spending for COX-2's, should we be giving opioids chronically.

Function makes a difference in these questions, and we need to know more about it, but I think we are suggesting to you that there be an additional carrot for this.

Does that capture what you are saying, Charles?

DR. McLESKEY: I am not sure, Mitchell, I am not sure that there is universal unanimous agreement that there would be three separate disease states studied in order to achieve a general claim.

I am one guy representing, obviously, trying to represent industry, but I work for one company, and I would suggest that before such a generalization or a statement like that of general acceptance were achieved, that there be some kind of working group formed where there would be representatives from several of the major players in this area to make sure we have consensus of that kind of an approach.

DR. FIRESTEIN: But it is important to remember that whether the number is three, you

know, three disease areas, or four, or two, or five or six or more, that the global pain indication should, by necessity, be a very high standard, because it needs to cross all mechanisms.

The question is whether it serves the clinicians well to have a global pain indication for a drug that does not work well in neuropathic pain, for instance, if you have done one or two other diseases or organ systems.

I think the bar is, by necessity, going to be high for global pain because that is in essence all pain under all conditions. It seems to me based on what I have heard today that there are lesser labeling criteria that still are very broad and still would be probably more reachable than we are today with current technology.

So, asking for all pain under all conditions when it hasn't been demonstrated is perhaps asking for something that is not really appropriate at this point.

DR. McLESKEY: I appreciate your comments. My only retort to that is that we need to balance incentives in order to advance the field versus the hurdles that are placed in order to achieve those goals, and that kind of a consensus development at

this stage, I would suggest needs input from some others who perhaps are not at this table.

DR. WOOD: Just to respond to this, I think it is important. I don't think we have consensus, at least certainly not from me, that the global pain indication would be required for approval.

So, I would visualize that a drug would come to the Agency and get approved perhaps with a more restricted label and could progress incrementally up that scale as experience, and so on, increased.

It would seem improbable to me that a company would go for a global pain indication as its first step. That would be an awfully high-risk strategy and one that would seem to me counterintuitive anyway.

So, I would be less concerned I think that you are, Charles, at the dangers of that, because you would only be going for a global pain indication once you had received approval for probably multiple other indications and had reasonable level of experience.

So, I think we are sort of arguing about something that is not likely to be even an early

step in drug development. Maybe I am wrong.

DR. FIRESTEIN: Why don't you go ahead and respond, and then Dr. Ashburn, and then we will probably move on.

DR. McLESKEY: Well, that is certainly a presumption that you have made, and there is actually a history, a recent history that global claims have been achieved, maybe with hurdles not quite so high, and again, obviously, the broader the claim can be, the greater the incentive there is for innovation from the sponsors.

All I am saying is that if we make the hurdle quite high or, as you say, if we have to incrementally approach it, the costs go up with that approach, and the resistance to innovation then may rise, which obviously, we don't want to see happen, as well. We want to encourage innovation.

DR. ASHBURN: I think the point that you make is something that one needs to bring out, flesh out a little bit more, and that is, is that if you make a global claim too difficult, then companies I think tend to go for a very narrow focus or very narrow indication to get a product on market with the expectation that that product for

pain will be used in a wider range of patients, so as an off-label use, and that has a double-edged sword, that if you make the bar too high, people go for a narrow indication. Then, the medication will be released, and then it will be used in patients in whom it has not been studied.

Not only is that a problem with regard to lack of good outcome data to guide clinical judgment, but also has a problem with regard to safety. That is one of the issues, trying to strike a balance, so that you encourage people who are developing products to widely study them the medication, but not make the barrier so high that they go for a narrow indication and actually increase the risk of harm to patients once a drug is released.

I also want to just re-flesh on the outcome measurement, is that I think it is a wonderful idea to include outcome measurement as a part of the clinical trials for these products. The concern that I have is that it is sending the voice that positive benefit in all those different fields are a requirement.

So, I think that tracking outcome measurement can be a vital important required part,

but I visualize that data being used to guide the development of the label rather than being a primary indicator for approvability.

DR. FIRESTEIN: Well, now that we have resolved this problem, I don't know that we answered the questions that you raised in No. 3 here by providing you with a list of appropriate models, but we did discuss No. 4 in some detail.

Again, just to reiterate, the notion is that there are still very broad claims that would still be available without a global pain indication, is that correct?

DR. SIMON: Correct.

DR. FIRESTEIN: At this point, we will move on to a discussion of back pain by Dr. Borenstein.

Back Pain - Chronic Issues

David Borenstein, M.D.

DR. BORENSTEIN: I wanted to thank the Advisory Committee and Lee Simon for asking me to speak today. He said I should make it practical, and I try to be a practical person, so hopefully, what I will speak to you today about in regards to back pain will, in fact, be practical.

It was one of the things I did want to

raise my hand and speak, but having the option of actually being able to speak and having the microphone allowed me to use it at this time.

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I just wanted to give you a little background about myself for those who may not know me. I am from the George Washington University Medical Center, not the other one across town. So, if you want to find me, that is where you will find me. I have been involved with low back pain in its various forms, both on clinical trials and from the standpoint of taking care of patients, I guess now about 24 years, so I think I have some experience at least in regards to low back pain.

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When the Advisory Committee and Lee asked me to speak, there were some issues that they wanted me to discuss, so I thought I would sort of put them out and say what they were in one form, but what they also truly meant, and that was to find the forms of chronic low back pain and its prevalence.

What does that really mean? Is it frequent enough and important enough to study? If we have it, it's a problem that everyone talks

about, but is it really big enough a problem for which it is worthwhile to actually look at?

Will patient selection including etiology and severity influence the performance of drugs in development? That means is it possible to identify and separate the individuals who have back pain.

This may be all moot if we can't really separate them out, they are just going to be one group of people, then, we may just need to discuss back pain, but there may be subgroups that we really want to identify.

Which are the appropriate outcome measures? That is, can improvements in back pain be related to therapy, in other words, can it be determined? If we have back pain patients and we treat them, can we actually tell whether we do anything for them?

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4. Will a general indication be useful for different labeling claims? I know Lee beat this up already, somatic versus neuropathic versus chronic headache. So, if you have someone who has pain, it's in the low back, will it, in fact, translate to them as far as their headache is concerned, will there be some applicability?

Finally, with chronic low back pain, will it serve as a measure for efficacy for a general chronic pain indication, or should it remain independent for a specific disease, exactly what we have been discussing this morning?

I don't know if I have all the answers for it, but I figured I would be discussing them and at least I will give you my point of view.

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So, what is chronic low back pain, what does that mean, and what is its prevalence? How often does it occur?

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Well, in a lot of different studies, low back pain is described as the pain that occurs in the area with boundaries between the lowest and the crease of the buttocks. So, when we talk about low back pain, we are really not talking about leg pain, we are not talking about sciatica, although that is part of what we see with low back pain, so depending upon how you define it, one can have a wide variety of people.

If you just define chronic low back pain, this would be the anatomic area that you might want to study. That doesn't mean you wouldn't

necessarily study individuals with sciatica, but that might be a special group.

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What is chronic low back pain? It has a duration. Duration may be as defined previously up to three months, that is, up three months there is this opportunity of having a repair, being in this acute nociceptive stage, so that the body may heal itself and then go back to its baseline state.

However, after possibly three months, maybe sooner, this neuroplasticity has occurred and thereby you are in a state where the nervous system has had a response to this injury and you are now in a chronic pain state.

Others have described chronic pain as pain that persists longer than the expected period of time for healing, so some people have described chronic pain occurring within two days or two weeks, not even waiting two months to be in a more chronic stage because it is no longer in this acute healing phase.

So, once again, these are at least two different definitions that one might want to describe in regard to chronic low back pain.

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What is its epidemiology? Is it worthwhile to study? Is it frequent enough, will you find people who would want to be in clinical trials because of this problem?

Well, 20 percent of the U.S. population develops back pain yearly, so 1 out of 5 is a potential candidate for a clinical trial. That doesn't mean all of them have chronic low back pain, but certainly 1 out of 5 do develop it.

Back pain is the second most common cause of disability in the United States, and it is the most common among men, accounting for 16.5 percent total disabilities in individuals greater than 18 years of age in 1999. So, I propose that it is an important problem. Not only does it cause pain, but it also causes disability, and it's expensive.

If you look at Workers' Compensation claims, which is far from all the individuals with low back pain, from 1986 to 1996, during this one-year period of time, 8.8 percent of the claims were for back pain, but was up to almost 85 percent of the costs.

So, having better therapies for low back pain is important. Not only it a frequent problem, but it also is potentially disabling and

significantly expensive.

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So, there are at least reasons for which having better therapies would result in betterment to the individuals with it and society in general.

Is there a fiction as regards to how low back pain does over time? In other words, the usual story has been that most patients get better within a two-month period, so we don't have very many going on to a chronic phase.

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Well, this study was done and reported in the Annals of Rheumatic Disease back in 1998. This was done in the Netherlands where they had individuals who were a bit younger, those individuals who we might want to think about being involved with low back pain. They had about 450 individuals where they sent out postal questionnaires over a 12-month period and followed them over time to see what happened.

Most people, in fact, got better. The median was about 7 weeks. However, still, at 3 months, 1 out of 3 still had back pain. You say, well, they still might get better. If you want to know whether these individuals will still be there

one year later, this study would suggest 1 out of 10.

So, with the individuals who have low back pain, 1 out of 10 in general will still be having it one year later. So, we do, in fact, have individuals who are available to be studied. You have, if you think of at least 2 percent, let's say, of the U.S. population each year going into the chronic back pain category.

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Now, it's very funny to me, when people ask me what is back pain, having written a 700-page book on it, it is very difficult for me to answer, and so when I hear people saying chronic back pain, I just go twirling around saying which one do you mean.

In my book that I wrote on this, we had 60 different reasons for developing the symptom, the symptom of low back pain. Now, it takes a little time to figure which disease is causing that, and we will talk about whether we are good at that or not, but this is one of the ways one might look at the various categories with low back pain, whether it's mechanical, rheumatologic, infectious, psychiatric, so there are a wide variety of

disorders which can be associated with this problem.

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Now, let's simplify it a little bit. What turns out to be the case is that the systemic, the rheumatologic, the endocrinologic, the psychiatric types of illness associated with low back pain are, in fact, relatively few.

This is probably being generous on the low side. Probably mechanical pain may be more like 90 or 95 percent of all the individuals looking at a large enough population of individuals. So, mechanical low back pain can be defined as one of these various problems.

It can be associated with disorders dealing with the muscle, ligaments, or tendons which have been injured. It can be discogenic, it can be the intervertebral disk which has been affected, and that is a whole separate topic of whether that causes pain or not, but can be associated with a herniated disc which may also result in a radiculopathy or sciatica.

There is also apophyseal joint disease, and I am sure that Dr. Brandt would agree that osteoarthritis affects the lumbar spine, so there

is some osteoarthritis there, as well. There is spinal stenosis, spondylolysis, and spondylolisthesis, which is an instability of the spine, and then scoliosis can, in fact, be associated with chronic low back pain.

These can all occur acutely. Some are more associated with a more chronic situation. So, you can have some that are acute and some, then, that will go on to the chronic phase.

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I would certainly like to hear what Dr. Woolf has to say about my sources of pain as regards to the lumbar spine. My suggestion is it is once again complicated as to which structures are being affected.

Superficial somatic, I love when comes in as far as the back is concerned. I can pick up herpes zoster and cellulitis pretty easily, and that is easy to do. It gets more complicated the deeper in the body you go, and that is why this is so complicated because we are very good at osteoarthritis of the fingers, but it becomes much more difficult when it is osteoarthritis of the zygo-apophyseal joints, because we can't get our fingers around them. It becomes much more

difficult to diagnose.

So, deep somatic structures, such as the muscles, the joints, the bursa, and fascia, also have a characteristic kind of pain, which I would propose is different than superficial somatic pain in its character, in its clinical symptoms.

The same for radicular pain associated with nerve root difficulties compared to visceral referred pain mediated through sympathetic afferents versus neurogenic pain, which may be more of this diabetic neuropathy or amyotrophy, psychogenic pain, which exists totally in the cerebral cortex.

So, when you deal with low back pain, depending upon which structures may be affected, and which nerves may be affected, you can get a different character of pain. I truly believe that I can tell the difference between somatic and radicular.

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It was also suggested that we have difficulty in deciding what pain intensity is, and I was always quite interested in knowing what minimal, mild, moderate, and severe was. Dr. Simon's definition was he gets it as soon as he

even gets close to the dentist's office.

Well, this is the way I decide about it because we don't have any specific machine that measures it specifically. I do it on the basis of function, and this is what I do in the office every day.

Minimal is mentioned in passing and its normal function. The person came in because they had knee pain, but when you go through your total review of systems, they mention that their back bothered them once in a while.

Mild is a component of symptoms with mild dysfunction. They are concerned that they are not running as far as they used to because their back bothers them. That is starting to concern them. It doesn't bother them with the rest of their activities, it is their recreational activities.

Moderate, it is getting in the way of what they do with their work, it is becoming an impact upon how they do their daily lives, and severe, the point that Dr. Simon didn't tell you, is that he brings his wife with him when he goes to the dentist because he will need someone to help him put on his clothes after he gets done.

That is the equivalent when I have someone

with severe back pain who comes to me, they come with someone else, because they can't function to put on their clothes to get in the office or to get out of it.

So, there are ways of differentiating among the various types of discomfort these individuals experience.

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The diagnosis of back pain is nonspecific in 80 percent of patients. This is a dictum which is repeated again and again and again, and it is based upon some studies which been in the literature for quite a long period of time, really before there was an MRI or CT scan.

It is easier to just repeat it as to go out and really find out if it's true or not, so it is repeated and said most of the time you really can't tell what is going on with these individuals. That might be a problem if you were going to base a whole indication on an entity which you really couldn't diagnose, and I could understand why that might be a problem.

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Is that truly what happens? There was just a very interesting paper, set of papers, which

appeared in the Archives of Internal Medicine just in the last month. It came perfectly on time in regard to this meeting.

Basically, it was a pro and con situation. What the authors were saying is specific diagnosis is possible or specific diagnosis is impossible.

On one side there was this physician, Dr. Abraham, who raised the point that, in fact, specific diagnoses are possible, that there are clinical symptoms and signs associated with differentiation of muscle, joint, and ligamentous structures, that it is possible to, in fact, differentiate mechanical versus systemic disorders, that you can categorize these clinical symptoms, that can be done, and that subtyping these individuals does have the possibility of improving therapy, that is, if you can separate the specific mechanisms either or pain generators or the nerves that are mediating it, might it be possible to get a better therapy because you could identify them.

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On the other side was Rich Deyo, and he has been long known for being of the school that you really can't make diagnoses. His point, however, his not hidden agenda, quite clear agenda,

he is concerned about individuals utilizing health services to make diagnoses, which don't really make a difference, so people doing MRI's and x-rays, and all this.

His point is specific diagnosis is impossible. You can find anatomic abnormalities in asymptomatic individuals. This will result in overutilization of imaging techniques. There is inconsistency with physical findings. In general, if we look at it, nonspecific therapy works, nonsteroidals can work in a wide variety of things, so if they do, why bother to try and find the specific pain generator, they work in general.

My point is probably a mixture of both. I think both have points to be made for their side. I think it is possible to separate these individuals a bit better, and I think even Dr. Deyo in his response said yes, it probably is recognizing that his concern was about utilization, and not the fact that you couldn't diagnose some of these more specific problems.

So, I do think it is possible, but until we categorize and study a bit more specifically, we may not be able to come up with better therapies, and that is part of what this group needs to

decide, is that worthwhile, and that is what the committee will have to sort of deal with.

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Also, is it possible to differentiate among these various types of problems, can you do the difference between somatic, neuropathic, and radicular pains? Yes, they can be differentiated, and specific pain generators are difficult to identify, but localization is not essential for effective therapy.

So, my point would be this, that it is possible to categorize some of these individuals with chronic low back pain, you can put them in broad categories, and then you can study them to see, in fact, they are responsive to different types of therapies.

I think it is important to try and separate somatic versus radicular, but that doesn't mean they should be mutually exclusive, and some therapies may, in fact, work in both areas.

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Now, as my third point, are there pain outcome measures or low back pain measures which have been shown to be effective in picking up differences? Now, Dr. Strand is I am sure going to

do an excellent job talking about this tomorrow, and I am not stealing any of her thunder at all, because I am just going to go into this for a minute or two, because I don't want to tread too far afield.

But I do believe, at least as part of our discussion, do we have these outcome measures, do we have back-specific function measures, do we have pain measures, and do we have patient global satisfaction measures that make a difference?

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Well, back-specific function measures do exist, and these have been tested for a long period of time. They are the Roland Morris Disability Questionnaire and the Oswestry Disability Index.

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For those who may not be aware of them, I am just going to take one minute to just describe them to show you that they do, in fact, exist, they do function assessments as a means of telling how back pain patients are functioning and how they are doing.

There are 24 items from the Sickness Impact Profile. The functions that they pulled out affect back pain that day. The scores are added,

and this has been a validated and reproducible instrument for a number of years since it first came out in 1983, and has been associated with picking up differences and improvements in patients with low back pain on a function basis.

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Then, we have individuals who have been measured with the Oswestry Disability Index, and this is also a pain and function assessment. There are 10 sections on various functions with 6 levels of assessment in each.

They measure physical and social functions that day. They can once again be added up to 100, and have been validated and are reproducible instruments, as well. So, from the standpoint of function, we certainly have capabilities.

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In regards to pain assessments, I will leave it once again to others to describe whether these are the appropriate ones or whether there are others that are better in describing specific different types of pain.

One may have a general type of pain assessment tool, and if you have a specific character of pain, a neuropathic pain, or another

type of pain, one might use that specific tool, as well, in that specific circumstance.

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Then, in regards to global satisfaction, I would ask this group to strongly believe that a question to the patient asking how are you doing and are you doing better is a worthwhile outcome, and should always be, period, case closed.

It doesn't take too long to ask, it takes very little time to circle, but that is what I ask every day, and you can do it with smiley faces, you can do whichever which way you want, but that is what the patient cares around, do I feel better all over, and what was said in regards to toxicities and frequency of dosing and everything else all gets wrapped up into the way the patient feels.

So, I think whether they are satisfied with their therapy, very much, a little, mixed reviews, or I really hate it, really does get to a significant outcome as far as these studies are concerned, and I think it is a very simple question to ask, but a very important piece of information to know.

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Then, of course, optional measures are

also possible depending upon whether you think there is depression associated with these individuals with chronic pain. There is the general health status circumstance with SF-36 and various depression scales, I just picked out one.

This could be optional if you think depression is playing a significant role in regards to these chronic back pain patients.

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So, I do believe there are instruments that exist that measure the effect of drug interventions on chronic pain for function, pain, global satisfaction, and for general health status.

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Now, what was mentioned also is quite clear, that is, chronic pain therapy is multimodality. Depending upon how long it has been present, one may use one drug, two drugs, three drugs, four drugs. One may use a variety of other physical modalities, physical therapy, exercises, a wide range of things in order to take care of back pain.

I am not sure how one wants to deal with that in saying they need to be additive or have a baseline state and then take one aspect away and

seeing if substitution makes a difference, either making the patient go back to their baseline state or, in fact, improve upon their baseline state.

So, these are some of the therapies that are available as far as back pain is concerned.

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These are the therapies, the drug therapies associated with low back pain. I want you to know that I looked in the PDR to see if one had an indication for chronic low back pain. None. So every day that I work in the office, I have no indication for any of the drugs that I am using.

I feel comfort with that, but uneasy. I have to tell my patient if they are smart enough or willing enough to ask me is this indicated for this, the answer is not specifically, but I think you have a problem that will respond to this.

So, here is a wide range. This isn't my list, this is culled from a number of different papers and studies looking at what has been effective as far as chronic low back pain occurred. This has been nonsteroidals, muscle relaxants, analgesics, antidepressants, anticonvulsants, alpha-2 adrenergic agonists, and a miscellaneous group including the NUDA receptor antagonists.

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I am not going to go through all of these. Certainly many of you know them already. There are the nonsteroidals. This was recently reviewed in Spine in 2000, suggesting that these medications, in fact, do have benefits as far as chronic low back pain is concerned.

The ones that are short-lived, have short half-lifes, they can be used for the acute exacerbations that Dr. Sherrer was talking about, that if you have someone who has a baseline state, but has an acute exacerbation, one can use a short half-life nonsteroidal, long, sustained effects for long half-life medications, and certainly from the standpoint of COX-2 inhibitors, decreased toxicity because the people will be on drugs for extended periods of time is certainly an important indication and concern, that it may be good for a week or two, but when you are talking about one or two years, it is still going to be safe.

I am not suggesting that one needs to study it that long a period of time, but there are patients who are on these drugs for extended periods of time, so toxicity is something I am concerned about when I start these patients, but I

don't really know how long they are going to end up on them, but if they work, I keep using them.

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Then, there are, of course, the muscle relaxants as they have been described previously, and these are important adjuncts to therapy. If you wanted to see the effect of any one of these for longer than six months, I couldn't show you a study that really did that on any regular basis.

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Non-narcotic and narcotic medicines are all used in patients who have chronic low back pain depending upon their status.

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I am almost out of time, but I wanted to be practical. We have been very much talking about mechanisms and all. I deal with patients just like many of you, and I thought what I would do to end up my discussion today is live my life.

You have a few patients with chronic low back pain. This is what they are getting. This is a 52-year-old person who had a work-related myofascial injury in the lumbar spine. It is mild to moderate, she is still able to function. We changed her nonsteroidal to a diclofenac product.

She remained on her muscle relaxant when she has an acute exacerbation, so she can stay at work. She knows that she can dose with an extra short form of the medicine, and she knows that she is supposed to be on her exercise program in order to maintain her function.

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There is a 67-year-old person who has facet joint disease, has basically osteoarthritis as part of their chronic low back pain. This individual is treated with a COX-2 inhibitor and a muscle relaxant, and has been on this regimen for an extended period of time.

This, I would say was the mild to moderate chronic somatic type of pain.

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Then, I have another individual who has had a laminectomy, some of these are post-surgical individuals, who happens to have a fractured screw in his back, but he doesn't really want to get it taken out.

So, this individual, over time, and I have been taking care of him over 10 years, has gone through a variety of therapies now where he is now currently on a COX-2 inhibitor nortriptyline, a

fentanyl patch, and a short-acting narcotic when he has his acute exacerbations.

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Then, finally, for the individual who has moderate to severe neuropathic pain, who is still in this chronic back pain situation since he has a component of pain, he has had a traumatic neuropathy to the sciatic nerve.

He is on a long-acting nonsteroidal, gabapentin, oxycodone, long acting, and short-term narcotic for when he has an exacerbation.

That is what chronic low back pain therapy can be depending upon who you are seeing and what kind of status they are in. I do believe it is possible to separate these individuals out. Many of these individuals have been on a variety of therapies for an extended period of time.

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So, I would like to conclude with this and hopefully have answered some of these questions, but probably have raised more. I do think that chronic low back pain is a model for chronic pain. I think it is an important problem.

I think there are enough people in the society for which it is worthy of being

investigated. There are outcome tools available I think at this time that can at least give us a handle as to how to measure it, but certainly others, as they are developed, would be useful.

Somatic pain is identifiable, that is, pain related to musculoskeletal disorders, and for terms if you don't like somatic, but prefer musculoskeletal system, would be where I would put that, are identifiable and can be seen and studied.

The degree of pain and effect of study design I think is also possibly differentiated. For those who have mild to moderate pain, it might be possible to do a single drug versus placebo with an active comparator, however, when you have these individuals who have more severe pain where there may be more mechanisms involved, there, you may have individuals who may be on a stable multidrug, multimodality therapy, but there, take the drug away, have them flare, and then replace it with the study agent and thereby be able to determine whether they did better or worse from their baseline state.

That is where I will conclude. Thank you very much for your attention.

DR. FIRESTEIN: Thank you very much. We

have about 10 minutes to discuss Point No. 5, which is to comment on the value of chronic low back pain as a separate labeled indication versus part of a broader claim.

Discussion Point #5

DR. MAX: A question for Dr. Borenstein. One big distinction that seems to come out of your talk is the distinction between people who have low back pain every day for a year or two years and those who are having clear-cut, new injury, where perhaps the disc is getting another little tear, and all the studies, like the postcard study you show, had people with new relapses.

Do you think it would be appropriate in clinical trials to make some sort of distinction between these people who probably have some acute inflammatory pain on top of it, which might respond to different drugs and how would you do it?

DR. BORENSTEIN: Well, I do think it is possible to separate these individuals out. Some people have a chronic ongoing back pain, which it may vary a little bit, but is essentially there for extended periods of time. We are talking months and months and months.

There are other individuals who have

exacerbations of their pain, they wax and wane. Those individuals do have a different kind of story. Some of those may think it is the weather that bothers them or certain activities that will have an effect upon their pain.

So, I do think it is possible through the appropriate questions at the start of such a study to differentiate from these individuals who has a chronic stable type of pain versus those who are having acute exacerbations, which may have more an inflammatory component.

DR. MAX: Has the methodology been developed yet in any of the published clinical trials of back pain to distinguish these two classes?

DR. BORENSTEIN: Well, as I tried to show, there is great debate about whether one can define or describe low back pain, and this has just been written about last month. I think if people do take care of back pain patients, you can separate these individuals out.

There are a certain criteria where one might say their level of pain has remained at a certain level for a period of time. So, I do believe that it is possible to separate them out,

but has it been studied specifically as to which group this may be, whether it is osteoarthritis with more a flare component? No, that hasn't been done.

DR. FIRESTEIN: Dr. Sherrer.

DR. SHERRER: I think Dr. Borenstein has shown that low back pain has all the general problems that chronic pain has in general, and I don't think it is going to offer us anything specific.

You pointed out that you have osteoarthritis affecting the low back, you have inflammatory joint disease affecting the low back, you have soft tissue pain affecting the low back, and I think we see that clinically.

Then, you have the chronic persistent pain, the chronic intermittent pain. It is the same thing we see with chronic pain elsewhere. So, I don't see that separating low back pain out per se is going to be beneficial unless we are going to be able to separate out inflammatory low back pain or osteoarthritic low back pain.

DR. BORENSTEIN: My suggestion would be that we could. If you have a sed rate greater than 20, you have an inflammatory process which

separates out most, I do think it is possible to separate out those individuals who have inflammatory back pain.

I think we can separate out the spondyloarthropathies. Those people have infections, and all those. I would not suggest that it is so difficult to do. I think it is clearly possible to identify those individuals who have mechanical pain.

Now, if you want to separate out those who have it solely on muscle discomfort versus joint discomfort, it may become a bit more difficult, but from the standpoint of an inflammatory versus non-inflammatory standpoint, I think that is not a difficult process to undergo.

DR. GOLDKIND: I would like to ask Dr. Borenstein what evidentiary base are you familiar with that speaks to the polypharmacy, not surprising at all, but striking how patients with chronic low back pain, and that is probably going to be true in other chronic pain situations, are on polypharmacy, but is it fully anecdotal or do you see studies that incorporate that aspect.

DR. BORENSTEIN: Most of them are anecdotal. I mean it becomes most of the way drug

studies are done for the most part except in rheumatoid arthritis, and they haven't necessarily been transposed into chronic low back pain, is that you have a stable therapy, which can be on a wide variety of drugs, and then you take one drug away.

This, I do not believe has been specifically done in chronic back pain patients who are on more than one drug. That is the problem that we face. If this was thought to be a good process, then, in fact, that could be done, but that is the way some of these patients with chronic back pain need to be treated.

Some, in fact, can be treated with one or two drugs. Others with more severe pain are treated with multiple drugs.

DR. GOLDKIND: Do you think there would be any value in studying specifically combinations, how we put drugs together, or does the current clinical trial design where there is background that includes the remainder suffice for clinical practice?

DR. BORENSTEIN: Well, getting back to what Dr. Woolf was talking about before, this may be one of the ways of trying, in fact, to identify those individuals. Just hypothetically, you have a

group of people who are on a nonsteroidal, muscle relaxant, a tricyclic. You have three drugs.

You come along and find out that you intervened with one, you take one of those out and intervene and find a subgroup of people who have a specific response, this might be interesting in identifying those individuals who have a response to that specific group, because it is going to be very hard to find these people who have chronic back pain, who are going to be on placebo versus the active comparator, and nothing else.

So, I think this may be one of the ways of getting those drug trials done and also identifying those individuals who may be doing subgroup analysis to see how they may have responded above and beyond what the mean might have been otherwise to get at some of these mechanism problems.

DR. FIRESTEIN: Dr. Cush.

DR. CUSH: I think from Dr. Borenstein's comments we should be very concerned that despite the prevalence of the condition, the number of agents which have targeted back pain for an indication are very few, and that is surprising and disappointing.

I think that the FDA should make an effort

to try to make this an indication if, on one hand, to spur and excite research in this area as an indication, but obviously, this was always out there and people could have gone after it, and companies may have stayed clear of low back pain as an indication for a variety of reasons, maybe the difficulty in studying patients, the outcome measures, and whatnot, but this is an inherent problem in there and maybe the FDA can look forward to try to develop ways of pushing people in this direction as far as research and clinical trials.

One way might be for that global indication that we argued about in the last session, maybe one of the defining diseases under that heading might be low back pain.

MS. McBRAIR: As the consumer rep, I just wanted to thank Dr. Borenstein for supporting the idea of studying patient function, their patient global assessment, and possibly quality of life.

People can have a lot of pain medication and pain control, and not be able to function very well, as oftentimes noticed by employers and families and others, and I think we need to take a clear look at what we are doing to people when we offer them all these medications.

DR. FIRESTEIN: Dr. Brandt.

DR. BRANDT: Polypharmacy is not unique to low back pain. It may be a general phenomenon in patients who have chronic pain. In osteoarthritis, those people who are given a prescription NSAID, a very significant proportion are taking also an over-the-counter NSAID and acetaminophen and glucosamine. So, it is not unique to low back.

DR. BORENSTEIN: If I could just comment on that. Once again, although ideally from a scientific basis, it is nice to think of nice straight lines as the only way things happen, but dealing with human beings, they always find ways of making the lines curve.

I have never seen a straight one yet, and there is always a little bit of everything, and the trouble that we have is trying to identify those people and how they verge away from this line, this straight line, where the curves come in.

So, that is why I was saying polypharmacy, yes, there may be this peripheral sensitization and other things playing a role, as well as nociception. Some people may have some of both, and that even though it may be what we would expect, where a COX-2 or a nonsteroidal may have no

effect, in certain circumstances, they do seem to, and so we are always surprised, we are always happy it happens, but I can't really always explain it.

So, though knowing the basic science is clearly essential, and the better we get at it, the better we will be able to have therapies. At this point, I still think that we still have to use a little bit more leeway in the way we actually use these drugs to try and maximize the effect in our patients.

That is once again the basic goal is to make the patients better. The science will catch up with the human beings as they tell us how they are doing.

DR. FIRESTEIN: One of the problems with looking at low back pain as a single entity is that it becomes difficult to manage them with an individual agent for diseases, that has multiple etiologies, just as we don't have a single indication for heart disease, for instance, but we wouldn't necessarily even desire a single indication for low back pain, which is in part caused by osteoarthritis or other mechanical derangements, and the like, or neuropathic diseases.

I wonder if we would be doing the patients a service or a disservice by lumping all those patients together rather than trying to be more specific in targeting our approaches.

For instance, you already mentioned that 90 percent of the patients have mechanical issues, and that might be one way of at least getting one's arms around the indication rather than just trying to include all back pain.

DR. BORENSTEIN: My response with that would be exactly that. I think you can separate out these individuals who have musculoskeletal versus the systemic illnesses, and make a difference for those individuals.

It becomes difficult to say that it is only joint, and not muscle, because you can get referred pain, as well, so if you are able to deal with that process and make a difference, even though it may be muscle first and joint second, or joint first or and muscle second, you can still make an impact in this musculoskeletal arena.

DR. FIRESTEIN: Dr. Katz, and then we will finish up.

DR. KATZ: I would like to come down on the side of an entity of chronic low back pain.

Again, as Dr. Borenstein did, we are talking about non-neuropathic low back pain, we are talking about eliminating systemic diseases, but I would be in favor of that being an indication unto itself and also that being a disease model that could be used to work towards a musculoskeletal claim.

All of these diseases can be split infinitely into different subgroups that may respond more or less well. We just heard earlier that hypertension is actually a number of different diseases that respond differently, but nobody is bothered by the idea of having a drug for hypertension, diabetic neuropathy, it is the same.

Postherpetic neuralgia, it doesn't bother us to approve a drug that works at best in a third or 40 percent of patients, knowing that our approval only applies to a subgroup, but knowing equally well that because we don't know how to segregate out that subgroup, we need to provide a physician a reason to use the medication.

We also know that much more harm has been done by under-recognition and undertreatment of chronic pain than by overtreatment, so if we had to come down on which side we would want to occur, I would prefer to err on the side of seducing

physicians into treating their patients.

The fact that the chronic low back pain, even musculoskeletal pain is somewhat heterogeneous, I think is a strength in the sense that if you can show in a good trial that your medication works for this admittedly heterogeneous group of disorders, then, all the more it should be applicable to a broader musculoskeletal pain diagnosis where its heterogeneity is actually a strength, and not a weakness.

DR. FIRESTEIN: I would agree with that as long as we are primarily discussing mechanical back pain.

DR. KATZ: Yes, as Dr. Borenstein defined it.

DR. FIRESTEIN: That brings us to the end of this morning's session and we will reassemble at 1 o'clock. Thank you.

[Whereupon, at 12:02 p.m., the proceedings were recessed, to be resumed at 1:00 p.m.]

A F T E R N O O N  P R O C E E D I N G S

[1:05 p.m.]

DR. FIRESTEIN: The next segment is the open public hearing, which involved a number of individuals who will make short presentations from 5 to 10 minutes.

For those individuals that will have PowerPoint slides, I would ask you to make your presentation from up here if you already have them loaded onto the computer, and if you haven't already done that, then, you will not be making slide presentations unless you are very fast.

Again, the various individuals have already been apprised of the time limitations and while we don't have a gong up here to cut them off, I would ask them, please, to try to adhere to them as closely as possible.

The first is Dr. Najib Babul, Chief Scientific Officer of TheraQuest Biosciences.

Open Public Hearing

DR. BABUL: Good afternoon. I want to thank the Advisory Committee Chair and the Division Director for allowing me to speak at this meeting. I am particularly pleased to speak at this meeting because I think the briefing document raises a

number of important issues both to regulators and to drug development scientists.

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Let me just introduce myself briefly. My name is Najib Babul. I am Chief Scientific Officer for TheraQuest Biosciences, a Philadelphia, Pennsylvania based company, consulting in the area of analgesia rheumatology drug development.

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This is my conflict of interest statement, pharmaceutical sponsors that I work with, have submissions or pending submissions before Division 550 or Division 170, and the views that I express are solely those of TheraQuest Biosciences.

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Much has been said earlier today about the regulatory framework for approval of drugs and what is lacking in the existing guidelines. Certainly I can tell you as somebody who has been using the 1992 Analgesic Guidelines that before we throw the baby away with the bathwater, these guidelines are fairly robust and certainly help those of us who are in the trenches and developing drugs for acute pain, these guidelines have been exceedingly useful and continue to be useful.

That is not to say that we don't presently have challenges in drug development. In addition to these FDA guidelines, there is the CPMP document, draft document, which also provides additional guidance to those of us who are doing international clinical trials in analgesia.

Of course, we have rather well put together OA guidance document from the FDA and from the CPMP, which can provide a bit of a foundation for going forward if a decision is made to put together additional guidance documents.

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Now, having said that, there are certainly gaps in the regulatory framework for development of analgesics. This is a short list of some of the gaps as I see them, and the include multi-dose evaluation in acute pain, evaluation of drugs with slow onset of effect in acute pain, and there are clearly some drugs, including drugs that have a depot effect, that provide sustained analgesia in the perioperative period, for instance, that would fit into that category.

Drugs for neuropathic pain, which was the subject of a separate Advisory Committee meeting in May, drugs for cancer pain, which perhaps fit in

the mandate of this Advisory Committee, and, of course, the possibility of putting together guidance documents for low back pain, for fibromyalgia, and for myofascial pain, then, broadly speaking, looking at chronic pain as an indication.

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This is a brief list of some of the models of chronic pain. One can categorize chronic pain in a number of different ways - mechanistically, by diagnosis, etiology, et cetera, and this is an attempt at categorizing some of the models, myofascial pain, low back pain, osteoarthritis, fibromyalgia, some have argued and actually demonstrated successfully that mixed model populations with chronic non-cancer pain can be successfully evaluated as a heterogeneous population, and then, of course, neuropathic chronic pain and cancer pain.

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Now, there are some compelling reasons why we have lagged behind in chronic pain in contrast to acute pain in developing guidelines and in developing drugs and getting a label claim. I should note that there is a bit of a divergence in

terms of the labeling history for opioids, particularly sustained release opioids in the Division of Anesthetic Critical Care, Addiction Drug Products, where there has been a de facto chronic pain indication without stating chronic pain, and in the Anti-inflammatory, Ophthalmic, Analgesics Group where, in fact, that indication I don't believe has broadly existed although clearly there are some drugs historically that have been approved for the treatment of moderate to severe pain implying acute and chronic.

Now, some of the challenges that drug developers like myself find in developing drugs for chronic pain is that the etiology is rather diverse. Dr. Borenstein earlier talked about I think 60 or 70 potential etiologies for low back pain alone, so certainly even with a heterogeneous, a seemingly identical "diagnosis," broadly speaking, or presenting a complaint like low back pain, you can have a rather heterogeneous population.

Having said that, perhaps much more is made of that than we ought to. A substantial number of patients, as Dr. Borenstein noted, have mechanical low back pain, and while there is some

disagreement, many have argued that as many as 90 percent of patients with low back pain have idiopathic low back pain, and there is now pharmacologic evidence from work that has been done demonstrating that that group, whether it is homogenous or heterogeneous, in fact, is a worthwhile group to evaluate analgesics in, and we have certainly been able to separate active from placebo.

In addition, these patients have considerable amount of psychological overlay which varies a great deal from patients who may have some myofascial pain post-motor vehicle accidents to patients with osteoarthritis who may have considerably less access to diagnosis.

We also have a situation that is confounded by disability payments and litigation and secondary gain issues which make it very difficult for us to look at issues of function, for instance, in this population.

I think, finally, there are unrealistic outcome expectations. There are a number of stakeholders in this debate, not just drug developers and regulators. In fact, insurance companies and other third parties sometimes view a

successful outcome not as relief of pain per see, but a return to work situation, which of course means that their exposure to liability, financial liability is significantly reduced.

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Recently, Division 550 has suggested that replicate evidence in three chronic pain states or chronic pain models are necessary for a chronic pain indication. While I appreciate that the brief document suggests to the committee that this is subject to consideration and some debate, and that it is not cast in stone, I think, Dr. Simon, you referred to this as an iterative process, there are some potential implications that I think we need to consider.

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I think the first issue that concerns me is that there may be an absence of established models to provide evidence in three chronic pain states. While one can throw fibromyalgia into this chronic pain basket, some would argue that, in fact, it is a rather distinct entity and that it may not respond to many of the agents that other drugs perhaps respond to in chronic pain.

I think certainly the suggestion contained

in the briefing document and indeed at the NIH-FDA Workshop, that replicate evidence for a specific sub-indication would be a basis for approval is reasonable. I think that very few would disagree that at least in a 505(b)(1)/ new chemical entity approval strategy, that if you are going to go for a specific sub-indication, that perhaps some degree of replication is necessary.

However, I would suggest to the division and to the committee that replication across three models, models, which we have yet to fully establish and validate, might be too onerous a requirement to put on the pharmaceutical sponsors, and that perhaps, and this is a suggestion for potential discussion by the committee and by the division, that perhaps replication in two models of chronic pain or perhaps robust and internally consistent evidence in single trials in three models might be sufficient to provide a broad indication of chronic pain with the proviso that the Clinical Pharmacology Section of the package insert would speak to the specific evidence that is available on that drug.

One concern that a number of us interested in chronic pain have is that if the burden is too

high for a broad indication, we may end up people being expeditious, and there was some reference to this earlier, people just taking the quick and dirty route out, just getting a specific narrow sub-indication with the potential for substantial off-label use and orphaning of other indications for evaluation purposes.

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There are a number of additional issues which I would like to just very briefly address. In the briefing document, there is reference to the use of co-primary endpoints. Indeed, pain function and patient global are important endpoints. There is little debate on this issue, and I believe Dr. Strand at the NIH-FDA Workshop led a breakout session on this particular issue, and there was general consensus that these are important endpoints.

There is indeed some precedents at least at the division in terms of for OA, in terms of having a win on three co-primaries, however, it does increase the statistical burden required for approval, and I think that for function, function the way it is viewed through self-reports, we need to be careful that we define function carefully

because function, the way it is viewed, say, in OA, using WOMAC as an instrument, is very different than the way function is viewed by pain physicians.

So, before talking about function as a self-report, perhaps that may be achievable, although I am not certain about that, in all chronic pain states. Certainly, we don't ask that in depression, we don't ask that in migraine in terms of return to work or restoration of function per se, and that it may be too unrealistic a pharmacologic expectation to put on what is really a complex disorder, and I would ask the Division and the Advisory Board to consider this.

DR. FIRESTEIN: Dr. Babul, could you wrap up, please.

DR. BABUL: I am pleased to note the Division was prepared to consider placebo versus active control, that have some assay sensitivity.

I would urge the Division to consider some clinometric flexibility, so that we don't have ossification of trial design methodology. Finally, I would suggest that we need some degree of harmonization to the extent we can between Division 170 and Division 550 as we go forward in terms of approaches that are acceptable for opioids and for

non-opioid analgesics.

Thank you.

DR. FIRESTEIN: Thank you.

The next speaker is Dr. Kenneth Verburg, Vice President, Clinical Research, Pharmacia.

DR. VERBURG: Good afternoon. My name is Ken Verburg. I am here representing Pharmacia Corporation today. We appreciate the opportunity to contribute to the meeting.

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I would like to limit my comments and my brief presentation today to just some general observations about the development of new guidelines for analgesics or drugs intended for the treatment of pain, and then focus on some observations specifically directed towards chronic pain and acute pain.

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As we heard this morning, it makes at least some sense based on the information we have at hand to set up and use a mechanistic basis as a framework at least for the indications or the way that we think the indications should be laid out.

This would lead to using this particular mind-set, an easy separation if you will, of

nociceptive and neuropathic pain, but a subdivision of nociceptic pain into somatic and visceral pain is not quite so clear with both being acute and chronic, and substantial overlap between the two conditions.

Also, we could use a mechanistic basis, as we have heard this morning, about the chronicity of pain, separating out acute and chronic pain into separate indications, and not necessarily having to have or having to demonstrate acute pain a priori before getting an indication for chronic pain.

We could also use mechanisms to gauge pain severity. Particularly here, I think, we are most interested in the differences across models and how that might translate to effective regimens, and finally, in terms of just general overall considerations, a notion or a realization that there are different classes of analgesics that may be effective as either monotherapy or multimodal therapy under certain conditions in the particular sites of action.

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We would also encourage that the development programs expedite therapies to meet the clear unmet medical need in this particular area,

that efficient programs are set up that provide the information that is needed for registration, cut down on the white space with the gray area that us, as sponsors, sometimes confront, and also that we consider conditions of clinical practice, that being preoperative administration or preemptive administration and/or postoperative administration, multimodal analgesic regimens for certain conditions, and also differences in the treatment of acute and chronic pain.

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Some comments now about chronic pain specifically as the previous presenter outlined. These are the models that we have the most experience in, but limited in terms of their duration in 12 weeks or longer, primarily to the arthritides or osteoarthritis and rheumatoid arthritis. You find very rare cases or even nonexistent, that the other conditions have been studied beyond one or two weeks.

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In terms of the approach to the determination of efficacy, we have used successfully the three-domain approach in both osteo and rheumatoid arthritis, which would include

pain intensity, a global assessment and functional or disability assessments, and are pushing forward into chronic low back pain using specific instruments for those conditions, but again using the three-domain approach.

As was mentioned this morning, however, this approach may not be applicable to all conditions. Our experience in cancer pain, albeit limited, we have experienced difficulty in showing functional improvement in combination with improved global or pain severity scores.

As I mentioned before, on the previous slide, there is a limited number of models, at least in our hands, that would appear to be suitable for the study of three months, and even those that may be approachable for this duration of time, you are always left with the dilemma of what to do with patients on extended placebo treatment, how to handle that both in the clinical trial, as well as the statistical imputation that results.

Also, we would like to propose that serious consideration be given to models of chronic intermittent pain, what particular endpoints might be useful, the duration of treatment, and/or the numbers of cycles that would be needed to be

treated.

Finally, we need to clearly outline as Dr. Witter mentioned this morning, the safety requirements for chronic pain in much more detail than the current guidelines now described.

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Due to the heterogeneous nature of chronic pain conditions, as we have heard this morning, we have also proposed a tiered approach slightly different than Dr. Simon had outlined this morning, but we would also agree that a separate indication for each condition with replicate studies would seem to be of benefit.

An indication for chronic musculoskeletal pain, we would propose could be achieved with a single study in three chronic musculoskeletal conditions, in a sense, a replication would be achieved, as well as spreading out the observations, if you will, across a number of musculoskeletal conditions.

Finally, we would propose that a way forward for a general chronic pain indication would be a single study in two chronic musculoskeletal models and/or cancer pain, and a single study in two neuropathic models, again tracing back t the

differences in the mechanisms at least as we best have them identified now. This would seem to fit very well with that particular model and the limitations.

I just want to make a couple simple points here. One model does not achieve all necessary objectives, in particular, demonstrating acute onset of analgesia is difficult in some of these models due to the high placebo response and the self-limiting nature of the pain often confounds demonstration of effective regimens, particularly on the days 2 and beyond.

It is also very variable as to what an effective regimen might be depending on the model that is selected, so we would advocate that studies with multiple doses over a number of days be conducted in both musculoskeletal conditions, as well as post-surgical conditions.

Finally, one additional comment particularly related to primary dysmenorrhea. This is sort of an orphan here. It is a stand-alone indication, however, data from this particular model has been used in many cases to support an overall acute pain claim, particularly with respect to onset of action.

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While the current guidelines provide adequate criteria in our view to evaluate single-dose analgesic efficacy, it is traditionally understood that replicate studies in dental pain and post-surgical pain are required.

There are well-defined efficacy measures assessing onset, extent, and the duration of analgesia. Again, it is generally understood that the time to onset of analgesia should be demonstrated to be less than one hour in replicate trials, and that the time to rescue medication from single-dose studies is used to support the dose regimen on day one and subsequent days.

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The criteria to demonstrate multiple-dose efficacy, i.e., an effective regimen, are less well defined by the current guidelines, however, and that is where significant work I think needs to be focused.

Also, while we are doing this, study design and study conduct considerations are also important to bring into the mix, and that includes, as I mentioned before, the self-limiting nature of the pain in some models and also that the severity

of the initial pain in other models may not be controlled by monotherapy alone.

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Just to give you a little example of the self-limiting nature of pain, this is data from a thinly disguised COX-2 specific inhibitor trial in laparoscopic cholecystectomy looking at the percent of patients with moderate to severe pain plotted on the Y axis versus the days post-surgery on the X axis.

Here, you can see significant treatment effects on days 2 and 3, but overall by day 4, and particularly by day 5 and beyond, you can see that the numbers of patients experiencing moderate to severe pain even in the placebo group is quite small and does not allow adequate assay sensitivity to see a drug effect.

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Finally, just a comment about multimodal analgesia, obviously, the premise here is to obtain additional clinical benefit by controlling pain with agents from two to more classes. Ideally, these would be operating through different mechanisms or at least different sites, and the efficacy measures versus monotherapy would be

reduced medication requirements, improved analgesia over monotherapy, a reduction in adverse effects, and improved patients global assessments.

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Again, just to give you a little taste of what that looks like, this is from a total knee arthroplasty study looking at morphine alone here in the white line down at the bottom, and then two doses of a COX-2 specific inhibitor in the blue line at the full therapeutic dose, and in the yellow line, at half-maximal therapeutic dose.

You see that there are significant improved analgesia scores in terms of reduction in pain intensity with both doses versus morphine alone.

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One acute pain model does not fill all criteria for determination of a single dose and multiple dose efficacy, and we would propose that new guidelines specify in more detail which models are best to define onset, peak effect, and duration, specify compartmental approaches perhaps for pain studies, for example, single dose, multiple dose studies on day one and subsequent days, and then propose models best for monotherapy

versus combination therapy.

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Finally, specify what acute pain models are needed to obtain a broad acute pain indication by severity and/or etiology. We have spoken about that in the context of chronic pain today, and I suspect some of the same conversation will surface tomorrow.

Specify how many models and whether replication is needed in each. If models are of similar etiology, we would propose that really only one model should need replication in that particular instance.

Finally, as was my comment with chronic pain, we need to more carefully define the safety requirements for acute pain with a new agent, either when studied alone and/or in combination with pursuit of a chronic pain indication.

Thank you.

DR. FIRESTEIN: Thank you. Could you clarify just one point, and that is, for the chronic pain indication, the alternative proposal, two studies and three models is one study and four models?

DR. VERBURG: Yes, I was proposing one

study across four different models.

DR. FIRESTEIN: So, there would be fewer studies for each individual indication, but an increase in the number of total indications examined for the chronic pain?

DR. VERBURG: Yes.

DR. FIRESTEIN: Thank you.

The next speaker is Eugene Laska, Director of Statistical Sciences Division, Nathan Kline Institute for Psychiatric Research, sponsored by Merck Research Laboratories.

DR. LASKA: The business of doing clinical trials in the context of randomized, double-blinded clinical trials is to develop inferences that are causal, to be able to claim that the reason we see drug differences are because the different treatments that were in the trial were causal.

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As a consequence, any of the decisions made in terms of what must be demonstrated to get a claim has to be done within that context. We have not spent a lot of time this morning, some of the speakers before me have, on the details of clinical trial design and methodology, and I think that both the beauty and the devil are in those details.