is inconsistent drug effect. In this situation, none of the single measurements can really describe drug benefit for one over the other.

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When there are missing values, for the end of the trial measurements, the last observation carried forward is a commonly used imputation method. It imputes measurement at withdrawal time to later period.

For time-weighted average, one would say that there is there is no imputation as long as there is at least one post-baseline measurement, but actually, it is not true.

When the patient dropped out earlier, the average treatment effect before withdrawal time will be used to represent the average effect in overall treatment period. So, this is a form of imputation.

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Both of the imputation methods imply assumptions that later evaluations of drug efficacy is similar to that of earlier evaluation. This is a very artificial assumption, and cannot be verified by data we have seen.

Also, the results generally favor drug

with imputation than without imputation due to different dropout mechanisms in treatment groups, for example, different dropout rates and dropout reasons.

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We have seen those problems with imputation methods. Can we make any improvements in terms of trial design and data analysis? First, I think we should continue efficacy evaluation even after a patient drops out even the patient is on rescue medication, and these measurements can provide additional treatment information, so a true ITT analysis can be performed.

Also, if a clinically sensible responder analysis can be performed like a definition can be found, now, we can perform responder analysis in terms of time to respond, percentage of responder, and duration of response.

A responder analysis may better characterize drug effect and avoid artificial imputation methods by taking into account of dropout status.

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Parallel issues in acute analgesia trials.

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In single-dose acute analgesia trial, we focus on onset, duration, and pain curves. For multiple-dose acute trial, we focus more on duration of effect.

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In single-dose trials, time-specific pain measurements provide more information about onset and duration, but time-weighted average measurements, such as some of pain intensity difference or some of pain relief and intensity difference do not.

So, in single-dose trials, we prefer more of the time-specific pain measurements over time-weighted average. In multiple-dose trials, time-specific measurements and time-weighted average face similar issues as those in chronic analgesia trials, so I will only focus on the imputation methods for time-specific pain measurements in single trials.

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The three commonly used methods we have seen for data imputation are these three - last-observation-carried- forward approach, baseline-observation-carried-forward, and worst-observation-carried-forward methods.

The last two methods are generally more conservative than the last-observation-carried-forward approach, but all these three approaches are very unrealistic by carrying forward earlier pain intensity scores into later period. This is against the self-limiting nature of acute pain.

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I will use this example to show the artificial effect of those imputation methods. This is not a real example, but it represents the common scenario we have seen in trials.

Suppose patients' pain was evaluated for 24 hours after dental surgery, and these two curves represent the mean pain intensity a long time for placebo and the treatment group. These are observed curves without any data imputation. Because of the short duration of dental pain, at the end of 24 hours, no matter how many patients left in the trial, the patients' pain will be very mild, so the mean scores approach zero.

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Now, if we use early pain intensity scores to impute later period, these two red curves represent the imputed curves for pain intensity,

and then we got the impression that at the end of the day, the patients are still in pain and also the drug is still effective over placebo, this artificial effect is caused by different dropout mechanism. Mainly it is because more placebo patients drop out in the early stage, and also most of those patients drop out due to lack of efficacy.

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In summary, for chronic analgesia trials, end-of-the-trial measurement and time-weighted average represent different aspects of drug effect, and consistency of drug benefit through the trial is always an important issue for review.

In acute analgesia trials, time-specific measurements are more informative than time-weighted average in single-dose trials.

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We should continue to measure efficacy even after patients withdraw, even after patient is on rescue medication, and these measurements can provide additional treatment information for drug effect.

Also, if we can come up with clinically sensible responder definition, we can carry out a responder analysis, which may better characterize

drug effect and avoid artificial imputation by taking into account the dropout status.

Thank you.

DR. FIRESTEIN: Thank you very much.

Open Discussion of Points #1, 2, 3, 4 and 5

DR. FIRESTEIN: Now, we come to the time at the end of the say where there is a spirited discussion, and we can resolve all of the issues that have been raised, so that the FDA can go ahead and make its formal recommendations.

Before we move ahead, I just wanted to try to briefly summarize some of the points that have been brought up and then open them up for discussion.

One of the issues was the notion of whether or not separate acute versus chronic pain indications has utility not only for drug development, but also for our patients compared with simply a single indication for pain, and also whether or not this should be more mechanism versus clinical indication oriented.

With regard to the chronic pain indication, a proposal was put on the table that this could potentially be achieved with a very high bar where three separate indications would be

looked at, each with two studies and each involving three separate domains.

Notably, there were a couple of alternatives that were proposed during the open discussion or the public forum, one involving two separate indications and then another involving four separate indications, but with only one study for each one.

Then, we talked about low back pain, whether or not that would be one of these potential clinical indications for chronic pain, and, in particular, whether or not all low back pain could be lumped together or whether or not there is some rationale for taking the vast majority, which is mechanical low back pain, and then using that as a separate location.

Finally, we have talked a bit about safety and the issues regarding dose and indication creep, as well as off-label use. That was raised a number of times.

So, those are I think the major issues that are before us right now.

DR. MAX: I would like to return to the issue of mechanism-based diagnosis and ask my FDA colleagues about some possible incentives for this.

If we go back to Dr. Woolf's talk, he mentioned several dozen molecules involved in pain processing, and actually, we could probably get very close to some mechanisms in patients right now, because imagine, let's say we have the results of a large chronic pain trial, say, in back pain with some novel drug that works on one of those new mechanisms, and overall, there is just nonsignificant trends towards efficacy.

However, it is already known that probably half a dozen of the molecules Clifford was talking about this morning have common human polymorphisms with two forms of the molecule, either one made in higher volume expressed with a molecule expressed more or with higher functioning levels of the molecule and with some very common people with less expression or less functional forms of the molecule.

So, what if the company could for a few cents an assay take all the pain molecules and characterize the patients as high functional or low functional for that, so what if they do that for a number of different molecules and found that if they just take the subset, say, with a hyperactive NMDA NR2B molecule function polymorphism, in those,

the drug really was effective.

So, now they have found by dredging a prospective mechanistic-based subset, so they come to you and say, okay, could we now go and do one more study and get approval for this, what might you say to a company like this?

DR. GOLDKIND: We might say a number of things. I think that the assay that would differentiate a responder or potential responder from a non-responder has to be something clinically available, so that a doctor can use that in guidance, so it has to be referable to the population. It wouldn't really help a doctor or patient if they didn't have that.

In terms of the evidentiary base, is an exploratory analysis adequately supportive of a prespecified primary outcome for a second trial, that has been used before. There is not a global answer to that question, but that is what you are describing is an analysis where a subpopulation is looked at and where you are exploring for an effect on subpopulation, and you identify one, and then you confirm that in a second study.

That, I would say is really dealt with on a case-by-case.

DR. MAX: With regard to that, I think, you know, the tests themselves now cost like about 25 cents a genotype, so the company might even provide that. To say just that you need one new trial for it, that sounds pretty encouraging, because if I just came up and dredged a database with a new hypothesis, I think your earlier guideline, Lee, would suggest you are starting from scratch and you should have two trials for replicate evidence for a new indication. So, if you said that, that would be very encouraging.

DR. SIMON: Well, let's be clear. I always like being clear. What we did propose was that mechanistic models that had clinical relevance would be acceptable without further definition of the number of trials that would be necessary. We don't know yet how to go about this. One could even envision that the argument could be that such a design would lead to a definition in only subpopulations, and it would not be extrapolatable to the general population.

The down side would be that. The up side would be, well, so what. You have identified a patient population that would respond, you have a clinically measurable test that is clinically

applicable and accessible to the treating clinician, so therefore, you can identify the patient that could potentially respond, and that should be something that should be rewarded.

We would believe that that should be rewarded. There is nothing in our presentation that precluded a unique way of going about this. All we suggested was in a traditional trial design, that the three-model, two-replicate, three co-primaries would be important.

But if a mechanism could be defined, could be reproducible, and could be clinically applicable and available, then, I think all bets are off.

DR. FIRESTEIN: I think the key point is that it must be clinically applicable.

DR. DAVIDOFF: I was going to say that I have a feeling that the statisticians in the room are having acute epigastric pain hearing that by dredging a single database, you can, in fact, have the basis for approval.

I would think that that should be handled with extreme caution and that there should be required at least one replication of a planned trial.

DR. WOOD: I would like to return to the

opiate sparing issue. I was very concerned that there has been absolutely no discussion of the underlying assumption in these studies, and the underlying assumption in these studies is that there is no alteration in the pharmacokinetics of the opiate induced by the co-administered drug.

That may seem somewhat obscure, but when you recognize that erythromycin would be an extraordinary effective opiate sparing drug if administered with fentenyl or that inducing codeine's metabolism to morphine would be extremely effective by some drug with no primary analgesic effect, or more subtle changes, like we can turn Imodium, the anti-diarrheal drug, into a very potent analgesic and a very potent opiate by simply inhibiting the transporter responsible for normally keeping it out of the brain.

The ability to have unrecognized effects that have nothing to do with analgesia, I think are substantial. In addition, some of the metabolites that are produced from these drugs produce toxicity, and if they accumulate or are induced, they are likely to produce side effects that may or may not be recognized as being due to the metabolites.

So, it seems to me that there is an absolute necessity in an opiate sparing trial that we have a standard that dictates that the drug does not produce some pharmacokinetic interaction. That is tough actually. It is relatively easy to define the obvious ones like the drug concentration in plasma doesn't increase.

It is much harder to do that in, for example, supposing Imodium was on the market--well, it is on the market over the counter--we can turn Imodium into an extraordinarily potent sensory acting opiate by simply administering drugs that inhibit the transporters.

That is not something you would spot from an obvious plasma concentration time profile. So, I think there is a great danger in an overly simplistic analysis of opiate sparing as an endpoint, and there needs to be independent data that demonstrates that the drug has analgesic effect on its own.

DR. FIRESTEIN: Maybe Dr. Katz can address that concern with regard to the pharmacokinetics and opiate tolerability, and then Dr. Farrar, if you had anything to add, that is.

DR. KATZ: I agree.

DR. FIRESTEIN: Thank you.

DR. FARRAR: I think the point about the use of opioid sparing as a potential measure is an important jumping-off point to consider what was brought up in the last two discussions, the last one in particular, which is that what is it we are trying to do here.

I would argue, as I think Dr. Katz did very nicely, that opioid sparing might be a nice way to at least think that maybe the drug has some effect, but ultimately, what we are interested in is making the patient better.

At the end of the day, whether you are using a specific protein that you assay to identify a group in which people get better, which I think is a great idea and hopefully will pan out, but at the end of the day, we really need to decide what it is when a patient gets better.

I would ask Mitchell, in terms of the situation that he is talking about, would you want a particular group to respond a lot or a little, does it matter whether you have got a BRAC gene, so that you have got a 90 percent chance of developing breast cancer or a 90 percent of responding to a drug, or does it matter whether you have got a 51

percent chance of responding to the drug, because I think no matter how we slice this and no matter how we look at it, at the end of the day, we are left with the issue of does it make the patient better or not.

You can use any statistical technique you like or you can use any analytic technique you like, you can use any assay technique you like, but we can't escape that issue.

In terms of the discussion today, we have talked about a lot of different mechanisms, and I wonder what these people's thoughts are on that.

DR. FIRESTEIN: Janet and then Dr. Katz.

DR. ELASHOFF: In terms of the data dredging to find a subgroup that you then test in that subgroup, and that that might be a very good way to find subgroups in which it does, in fact, work, from a statistical point of view, the likelihood of the second trial coming out should be pretty small because you are mainly picking up false positives with that kind of multiplicity of testing, so that it might be that the first 5, 10, 15 times somebody tries that, it doesn't pan out in the second trial.

DR. KATZ: I just wanted to add one more

point about the opiate sparing trials, because I don't want us to leave the discussion with having trivialized the opioid sparing. I mean there are a number of clinical scenarios in which you have to give the patients concomitant opioid therapy with whatever your analgesic of interest is.

For example, in the postoperative thoracotomy or postoperative pain setting, it would be unimaginable to not allow the patients to have access to opioids, and the setting of cancer pain would be another example.

So, you often have to co-administer your study drug with an opioid analgesic, and then opioid sparing is a natural thing to look at. So, having said that, there are reasons to look at opioid sparing, but the bottom line is that you still need to decide whether or not your patients are better on your study drug.

DR. WOOD: A patient would not be better on a study drug just because you inhibited fentenyl or fentenyl's metabolism. I mean that is exposing them to the same dosage exposure as they would have got from a higher opiate dose, and we need to make that distinction.

DR. FIRESTEIN: And the patient wouldn't

necessarily be better, they would just use less opiates.

DR. KATZ: That is exactly my point and that if it was just a pharmacokinetic interaction, presumably, the patients would be the same. Your outcome measures would fail to show in that case that your patient was better off despite the opioid reduction, and it should be considered a failed trial. That is what I am trying to say.

DR. FIRESTEIN: Lee.

DR. SIMON: In fact, that is the conundrum. We are confronted in proposals to look at the question of opioid sparing as a primary outcome, and the reason we ask the question for this debate was we don't know what to do with that, (a) we don't know what is minimally clinically important decrease - is a 3 mg decrease, a 30 mg decrease clinically important unless you tell us what the measures are that tell us that it is important, meaning is the patient more aware, are they able to walk faster, is the recovery postoperatively improved, is there less pneumonia, if, in fact, pneumonia is an issue.

These are the issues that have to be clinically relevant to make a measure, such as a

change in opioid use, important, and that discussion is no different than the one that was raised by Mitchell just before.

The measurement of a receptor change or whatever is really not different than the measurement in the change in how much morphine that one might use unless there is a change in the clinical relevance and an improvement to the patient care.

I just want to make it clear to Dr. Davidoff that we would not be looking at only one unique database for such an event. One would have to define clinical relevance by multiple databases.

Thank you.

DR. FIRESTEIN: Dr. Davidoff and then Dr. Brandt.

DR. DAVIDOFF: I was really just going to say essentially the same point about opiate sparing, that it might not be necessary to find better overall pain relief, but fewer side effects associated with it.

After all, some of the major distinction between antidepressants is not that there is overall better therapeutic efficacy between SSRIs and tricyclics, but that there are fewer side

effects.

DR. BRANDT: I think this whole discussion on opioid sparing is very interesting, but I would suggest that in the context of the meeting, it is perhaps a little too narrow, we could raise the same issues with regard to NSAID sparing or chronic NSAID use.

DR. SIMON: So, in that case, Dr. Brandt, would you propose that a primary outcome for a new, perhaps analgesic that would not have opioid effects and would not have the traditional effects one associates with the traditional nonsteroidal anti-inflammatory drugs, could use as an outcome measure for primary approval, the decrease in requirement for the rather ineffective nonsteroidal anti-inflammatory drugs?

DR. BRANDT: When you consider the side effects associated with NSAIDs, the answer is yes.

DR. WOOD: But only provided you have demonstrated it is not just due to a simple interaction.

DR. BRANDT: Surely.

DR. FARRAR: At the end of the day, it makes no difference if you reduce the opioid or the NSAID. What makes the difference is whether the

patient is better, and if they are better, as Dr. Davidoff was suggesting, because the side effects are better, that is better. It is not that they are using less of one drug or another drug.

It really doesn't matter. I mean I agree with you, and I am not arguing the issue about opioid sparing, I think opioid sparing is suggestive at best, and you clearly need to differentiate between the amount of opioid that they are actually taking orally and the amount absorbed and the amount that is reaching the active sites and the amount that is causing the effect, and there are lots of drugs in which you get the buildup of toxic byproducts, as well.

But at the end of the day, what you really need to know is whether that patient postsurgically had a better experience with the combination of drugs that you gave than if you didn't.

How you define better depends on the circumstances that you are looking at, but I think there are clearly lots of indicators that we can use to look to see what we should be measuring and how we should be measuring. But at the end of the day, the question is, is the patient better, would I want to give that patient that drug the next time

around because they said, you know, I had three surgeries so far, this was the best experience I had so far.

That was very true with epidural anesthesias. I mean there is absolutely no question that people post-op with thoracotomies did better because they were able to breathe better, et cetera, et cetera. How much opioid you gave them didn't make a difference.

DR. FIRESTEIN: Dr. Sherrer and then Dr. Anderson, Dr. Strand.

DR. SHERRER: I think that at the end of the day, it is, is the patient better. I think that is very important, but I also think we need to consider some of the social issues with the chronic use of opiates, that impact on whether the patients are actually better.

We have many patients who are afraid to take opiates because of the issue of addiction, and there are many physician who are afraid to prescribe opiates because of the issue of addiction, and the bottom line of that is it impacts on whether the patients are better, because if they are not going to take the drugs or if the drugs are there and the physicians are afraid to

use them, then, it is not going to make the patient better even if theoretically they could.

So, I think we do need to look at this issue of addiction and tolerance, and what is the relationship more, and what I am hearing is that we can't really define that well enough to do that, or at least we don't have measures of predicting or defining addiction.

I think that is very important. One of the major issues with the use of opiates and chronic pain is whether, despite those six studies that you showed us that suggest there is not addiction, there is still fear on behalf of physicians and patients that there is addiction and that tolerance itself may lead to addiction.

DR. ANDERSON: My concern is about what you were saying just now, about the patient, at the end of the day, the patient being better, and that if this was solely in terms of having fewer side effects, that was okay.

I didn't like that, I guess because, you know, side effects don't happen, you know, happen sporadically or should happen sporadically, but efficacy is something that one would hope would happen in a large proportion of patients.

Historically, the FDA has kept efficacy and safety, I mean they are linked, but they are not considered the same thing, and it bothers me that a drug combination could be considered could, not because it was efficacious, but just because it had fewer side effects. I may be misunderstanding what you are were saying.

DR. FIRESTEIN: In some cases, the side effects are mechanism based, and that is a situation where it would be optimal to lower the dose. So, for instance, with opiates, constipation or nausea or vomiting, those are clearly based on the pharmacology of the molecule, and so if one can get past those by using a lower dose, and using another adjunctive therapy, then, there would be some benefit to the patient.

Dr. Strand.

DR. STRAND: I would just like to say this reminds me of some steroid sparing discussions that some of us have had in the past, and it seems to me that it is all find and good if we can decrease the dose of opioids or the dose of steroids, but if, in fact, there isn't some benefit that is measurable in addition, in terms of patient-reported outcomes of efficacy and/or tolerability, then, I don't know

that we have demonstrated very much of anything.

The other point that I would like to make is that I think data dredging is not the way we are going to get approvals or try to look at different ways of approving products, say, in chronic pain, or possibly even subacute pain or whatever we are calling it, but there is room to develop these analyses from the Phase II data, particularly since there is much more emphasis on doing better Phase II trials, dose finding and dose interval finding or schedule.

From that point of view, one could, in fact, develop evidence-based, responder type of outcomes, or one could combine certain outcomes for a certain type of response in the Phase III trials. That has been done before.

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

DR. CUSH: My summary of what I heard today that I would hope that the Agency would take away is I think that we are probably still wedded to some of the methods of the past, and that would be acute and chronic indications and some of the primary outcome variables that have been used for those indications, but that we hear that the

science has come along and we would like to see mechanistic issues being raised, may be secondary outcomes measures where applicable, and that would be ideal as we move forward and designing better trials that mean something.

Secondly, I think that making low back pain a priority and either incentivizing that or requiring that in some way would be nice, and lastly, the words of Dr. Carr reminded me of something that Ted Pinkus said at a meeting that I think Lee and I were at, which is that as clinicians and biometricians we have done a good job in defining outcomes and coming up with acceptable measures, but we have missed the boat because we are still not at a point where clinical trials are approximating what goes on in the office, so clinicians and patients won't understand an ACR-20 or a WOMAC, and whatnot, and at the Agency, I think it could go more towards that direction, I think it would also further not only clinical trials, but patient care, as well.

DR. FARRAR: To take off from what was just said by Dr. Cush and perhaps try and persuade Dr. Anderson that there may be some aspects of this that don't apply to everyone.

I agree with you. I think, Dr. Cush, that making the trials understandable to the clinical circumstance is of paramount importance, so that when I, as a clinician, sit down with my patient, I know what to do, and I don't just know that patients got better on the WOMAC by an average of 4. I don't know what that means now, and I know what the WOMAC is, even use it.

I think, though, the issue that I wanted to bring up more specifically is that what Dr. Max was suggesting was not, I think, that data dredging should be used as the sole purpose or the sole way in which a drug should be approved, but that it be used as a hypothesis-generating event, and I think that makes sense.

Then, he was trying to see whether one trial after that would be enough in terms of stimulating that kind of research, and I agree that there is issues there on whether it is one or two can be debated.

What he was getting at, though, was that with a 50 by 50 slab of gel, you might be able to tell what the makeup of that patient is with regards to their response. This gets at what Dr. Anderson I think was saying was that, in fact, the

drug that we use has to be good for lots of people, and we are getting to the stage now where we are developing drugs, especially in neuropathic pain, perhaps not so much in arthritis, where individuals who respond to a single drug are a minority of the patients that we are treating.

You can look at that two ways. One is we just don't know how to predict who is going to respond, and that is very true. If we could predict who was going to respond, then, 100 percent of those patients would respond, but the clinical fact is that people see arthritis, they don't see the variance of the arthritis that we might able to see here.

People see pain. They don't see the variance and the subtleties of it that an expert might see, and they treat them with the medications that we have.

There are some very good examples in postherpetic neuralgia and diabetic neuropathy where drugs that are clearly effective worked in about a third of the patients treated. About a third of the patients got a moderate or better improvement. That is 1 out of 3 and if I am treating in the office, and only 1 out of 3 people

get better, I am might decide that is not the right drug.

On the other hand, I might look at it and say 1 out of 3 in something where nothing else has worked, that is really good. The same applies in arthritis in that there are clearly differences between the NSAIDs, and they are not as dramatic perhaps as the differences in the anticonvulsants, but there are differences, and it may be that one group responds better to one kind of NSAID and a different one to a different.

So, the idea that we have to somehow have a drug that works in 50 percent or 70 percent of our patients in clinical trials is not I think the issue. I think the issue is being able to identify the people in whom it does work, and it really works, not just a little, but it makes them really better.

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

DR. DIONNE: I have heard the phrase "end-of-the-day" mentioned a few times. I am struck by the fact that this is the end of the first day that was supposed to be devoted to chronic pain, and I have heard a minimum consensus

of opinion on some of the issues that were raised for the Agency, and I would be afraid that they might go back up Rockville Pike and disappear into the back room, so to speak, and come back in four years or 10 years, as Al Sunshine said it took last time, with a document that reads like the Ten Commandments.

I am wondering, is there room for discussion of the processes that might allow us to resolve some of these issues based on some sort of a scientific process rather than an opinion-based process.

For example, the 125 pain measurement scales that Dan Carr mentioned are ones that it would be hard to imagine we could sort through and just by opinion say these are the two or three that should work, yet, we are still using Category and VAS, which are as old as the drug classes we use to test them on, ignoring all the new technology, which might include the electronic diary we heard.

Other outcome measures, how would we go about getting at which ones are desirable, let alone grappling with the issues like analgesic combinations, what would be the criteria for those. That was an issue that raged all through the 80s.

I am not sure whether it got resolved or people just stopped trying to get combos of NSAIDs and opiates put together.

Is there room for some discussion of the process that the Agency might use to arrive at from where they are now to where they would be when a document appears?

DR. FIRESTEIN: Is there room, Dr. Simon?

DR. SIMON: There is always room at the table. I think that this meeting and two meetings that have been held by the Advisory Committee of 170, talking once about neuropathic pain and issues about opioids reflects the fact that we are very interested in dialoging with the community, the patient community, about these particular areas.

We are talking on a regular basis, and will be talking on a much more regular basis, with the individuals in the FDA who are interested in pain and issues regarding pain, particularly the other Division 170, and coming up with a consensus as much as we can as it relates to the various different products that we are assigned responsibility for, and those products that we can possibly imagine will be developed in the future, to then lead us towards a document.

Furthermore, there are discussions that are ongoing with the NIH about establishing a meeting to discuss outcome measures, both acute and chronic, addressing issues regarding function versus health-related quality of life that need to be addressed before we can put pen to paper to try to design and craft a document that will fulfill all the needs that we have been talking about just so long today, not the less tomorrow.

So, that is the process. The process has got a was to go. We have got more internal debate to do, more external debate to do, more to learn, and to address Ray's issue of going to the evidence and the science using the science as we interact with the group at the NIH, in understanding more about outcome measures as we did at the last March meeting. So, that is the process.

DR. FIRESTEIN: Steve.

DR. ABRAMSON: I guess part of the process I would like to express is that we have this dilemma of wanting, at the end of the day, to do the best globally for the patients, and yet we are confronted by very specific syndromes that differ, and we have an iterative process to get a global overarching kind of indication, but, in fact, that

iterative process is going to take a lot of very focused specific kinds of analyses of different pain syndromes, developing clinical criteria of those syndromes, the way we have done in other diseases, in OA, and outcome measures, as Mitchell was getting at, even prospectively looking at certain biomarkers in those areas.

So, I think it is a time of great opportunity to look at different pain syndromes, to use this new development of analgesics as a way to use the clinical trial tool to answer questions that are mechanistic.

Part of the dilemma, the conflict is that one does not want to get a global approach too early without this iterative process having been gone through to really understand these different diseases, which, in fact, are quite distinct one from another, even in the musculoskeletal, so that is just the process comment.

Going to back to Dr. Anderson's, and Dr. Katz mentioned this, and it is a very focused question, back to the opioid use as a surrogate endpoint. There is a difference I think between what is good for the patient at the end of the day versus the regulatory agencies need to determine

whether a drug is efficacious.

Absent the metabolic effects of opioid, metabolism, for example, and drug-drug interaction, the question still is, is opiate use a legitimate endpoint, primary, secondary, by which you can judge the efficacy of a new drug.

That doesn't mean whether the patient is better to be on one or two, and I think you alluded to this, but I am not sure sillet [ph] isn't a valid measure. I don't know about the area, but it is worth discussing, which is not the patient's contentedness with their combination of drugs, but whether it's a tool, an instrument to judge the validity of a new drug being presented to the FDA.

I am just curious what people think. I don't know if I want to open that up to discussion, it is just kind of a comment.

DR. FIRESTEIN: That is another major area of discussion in and of itself. One of the reasons that the Division gathered this meeting was to address certain specific questions, and as we are getting towards the end of the day, although it is only 1:30 in San Diego right now, so I am just waking up, I think.

From what I heard said, I don't know

whether or not it can at least try to offer some more concrete guidance or at least advice to the Division with regard to some of the key questions, and one is whether or not there is, in fact, utility to having acute and chronic pain as opposed to just pain as a potential indication.

It seems to me that that is not an unreasonable approach, and I was wondering if there is any additional discussion that would help sort that out or if people are relatively comfortable with that.

DR. ASHBURN: I would say yes with the caveat that the definition goes away from time lines with regard to duration of the pain, and kind of goes towards the acute versus chronic pain definitions that Dr. Woolf presented to us earlier this morning with regard to pain that is expected to be of short duration with some expectation that it goes away over time.

Again, that goes towards a concern that chronic pain states sometimes can be rapid onset and can deserve study and therapy early rather than late in their time line, and should not wait three or six months prior to being allowed to include patients for investigation, and the example, that

is, patients with postherpetic neuralgia or with cancer pain.

DR. FIRESTEIN: I think that is an excellent point, and again raises the question of an acute persistence pain and acute chronic--I don't know.

DR. ASHBURN: One terminology that comes to my mind when we talk to medical students about this concept is short-term pain versus long-term pain, and the perception of getting away from the terms acute and chronic, which mean different things to different people, but rather, the expectation of whether this pain is of short duration, of limited area, whether or not the expectation is, unless one intervenes on the patient's behalf, that the pain will persist over long periods of time.

DR. FIRESTEIN: Dr. Borenstein.

DR. BORENSTEIN: Well, one of the points I wanted to make is what happens in the clinical trial situation and what comes into the clinic. I think all the basic scientists would agree if you can attack pain early, you would like to keep it from becoming chronic, so intervening as early as possible in the process to keep that from happening

may have a mechanistic way of trying to keep chronic pain from appearing, but if the patient appears to you already with a process which seems to be chronic pain, then, I think what you may find to be effective there may be somewhat similar to what you would use in the very acute circumstance, but you may need more interventions at that point to really make a difference in that individual.

So, what you would do if you had someone who was your patient over time, you would treat them differently than you might if you find them later on in the process when you have them as your patient.

DR. FIRESTEIN: Brief comment from Dr. Farrar and then Dr. Katz.

DR. FARRAR: There are I think two important components of this, and very briefly, one is just to remind us that acute and chronic are time frames and that the acute pain and chronic pain does not necessarily imply acute treatment and chronic treatment, and I think that those two things are very different in terms of thinking about the safety of a drug and the overall use.

The second issue I think has been brought out before, but would suggest that what we are

really talking about is reversible pain versus non-reversible, and there are certainly syndromes which occur and can, as I was learning at lunch today, snake bites last an awfully long time. If you don't know what I am talking about, you will find out at dinner, I guess.

But the point is that there are pains that occur for a very long time, but are reversible and are treated aggressively, and there are acute types of pains best brought up I think by Clifford earlier, which is that, you know, trigeminal neuralgia is an acute pain that is very, very different than postsurgical pain.

I think that it is very important to differentiate, but we have to be careful about the way in which we do that.

DR. KATZ: I was going to make a similar point, I think, which is that when we think about treatment of acute pain, the way it actually works out very frequently in real life is that patients are actually treated for months often for their so-called acute pain, which we normally might think of as just a few days. Thoracotomy, you know, 50 percent of patients six months after a thoracotomy have moderate to severe pain, spinal fusion

surgery, the patients are often on analgesics for six months or a year, knee replacement, et cetera, et cetera.

So, I think it is also worthwhile keeping in mind that how is the medication likely going to be used in practice, and the trials that are done to support that use ought to have some relationship to the actual way that they are used.

DR. FIRESTEIN: A couple of more brief comments over here and then we will go to the next point.

DR. WOOLF: It seems to me, coming back to the issue of what encouragement we can give to the Agency in terms of development plans, we have heard from Dr. Farrar that 30 percent of these patients may respond to a certain treatment, and he has no way of predicting at the moment who those patients may be.

My plea would be that in any discussion with the industry in terms of any development plan, as we are in this transition mode from a rather empirical approach to the management of pain to one where mechanisms can be identified, is to try and get as much information as possible.

While, on the one hand, of course, we all

agree we want the patient to feel better and we need some global measure of that, but the point I was trying to make this morning was that there are many aspects of a pain that are simply ignored in trials and that may be very useful in terms of seeing whether patients do respond in different ways to different forms of therapy.

So, I think part of the process has to be not to prejudge and to try and gather as much information as possible from the patient as to what their pain is composed of and how different aspects of the pain respond to different therapies.

DR. DIONNE: I think Clifford just said what I was going to say, but let me just try to restate it. If the Agency is interested in mechanisms, and if we think the way to the future is having a better understanding of the mechanistic process by which a new drug works rather than just extrapolating from animal models which may or may not be relevant, would there be a possibility of developing some sort of incentive into the claim structure or the approval process that would give greater favorability to coming up with a rational study of the mechanism underlying an acute drug versus a chronic drug, so you might discover, in

fact, as has been stated all day, that some drugs may be actually acting on a chronic pain mechanism that may be starting at the first day or two, and this may have long-term benefit for preventing the pain a preemptive fashion rather than having to wait two or three months and then try a treatment that is ineffective because that mechanism is no longer active.

So, have some mechanistic approach built into the acute versus chronic studies that allows a little bit of information to be gathered, and the best way to harness the resources that the industry could bring to that, of course, would be to have some sort of incentive in the approval process for that.

DR. CALLAHAN: I was just going to say I think you made a compelling argument this morning about the mechanisms, but if we don't have the instruments to measure the components, is it fair to ask the industry to look at those components until those measurements are available, or should we go with the global and ask them to look at that sort of in a secondary fashion as they evaluate the new drugs that are coming on.

DR. FIRESTEIN: This really brings us to

the second question, and that is, whether one focuses on mechanism-based indications of clinical indications, and by and large, over the course of the day, most of the emphasis is that while mechanism-based indications are of tremendous interest, the science isn't there yet in order to use that as the touchstone for specific drug approvals, and that we still are relying primarily on clinical situations and clinical indications even at this point.

I was wondering if again there was any comment or disagreement for that. Did you want to comment on that?

DR. KATZ: I agree that right now it is premature to begin a drug development program for pain due to excitable nociceptors or central sensitization or something like that, but one has to be careful not to just by default allow any clinical classification system.

Some of them make a lot more sense than others. For example, the idea of having a medication for cancer pain makes no sense to me whatsoever, because some people with cancer pain have a brachial plexopathy from tumor invasion, some people have bone metastasis, some people have

visceral obstruction with almost no connection whatsoever.

So, to me, that would not make a lot of sense specifically because the mechanisms are so different among those different types of pain, so again, you can't forget the mechanism either, whereas, musculoskeletal pain, it seems to me that medications that work for one kind of musculoskeletal pain tend to work for another - osteoarthritis, rheumatoid arthritis, non-neuropathic low back pain, et cetera, I would suspect because the mechanisms are similar in those disorders.

I don't think that you can just allow any clinical classification system, but you can pick and choose from ones that make more sense.

DR. MAX: I just want to mention what I heard Lee Simon and Larry Goldkind saying a few minutes ago seemed very new, that they said that if they get some novel evidence about how can you reliably predict response with a new mechanistic test, they have the authority to approve it after the post-hoc searching with one new prospective trial, and since it so new and they don't have to maintain a level playing field when there aren't

many other things, every situation is unique, it sounds like it is a real green light for industry to try to be imaginative and scientifically creative. That is the first time I have heard that.

DR. FIRESTEIN: I would not overinterpret those comments.

[Laughter.]

DR. FIRESTEIN: It is clear that exciting new discoveries, novel targets that have clear proven efficacy in clinical situations can move very quickly into the clinic, into approval.

An example of that would be some of the TNF inhibitors for rheumatoid arthritis. Under those circumstances, I suspect that what you envision would be possible although I wouldn't dare speak on behalf of the Agency--well, I think I just did.

This actually brings us to the other sort of difficult problem, and that is the notion of if there is going to be a chronic type of indication, what is the benchmark for that. I don't know what the right answer is. We have a couple of different possibilities. I didn't know if anybody on the committee had specific recommendations.

From my own perspective, I was intrigued by the proposal of the four different indications with single studies, because if you are using chronic pain as the actual indication, then, you are not going for the separate indication of OA versus something else. You are using chronic pain as the indication, and the second confirmatory study would be in a different indication.

So, there is actually a rationale and maybe a middle road whereby you actually require fewer studies, but more indications.

I would want to know if anybody had a comment there.

DR. WOOD: As written here, it seems to me to be counterintuitive. It seems to me that to put a bar up that says you have to demonstrate, for example, response in low back pain and diabetic neuropathy and cancer pain, seemed to me to be counter to everything we have discussed in terms of mechanisms.

It would seem to me that demonstrating that a drug is effective in multiple indications demonstrates just that, that the drug is effective for multiple indications, and at that point, physicians can and do make decisions every day

about extending the drug's use into other indications for which it has not been tested.

But making the leap in terms of a labeling for indications for which it has not been tested seems to me something that has never been done in any other setting. I don't see even why you need to do it. If you have studied the drug in four indications, that is normally what you label it for.

Just to follow that up, the ACE inhibitors were all approved for the treatment of heart failure with subtle differences in the indications for which they were approved, reflecting the studies that were actually done.

That hasn't obviously affected their use in these indications.

DR. FIRESTEIN: Dr. Woolf and then Dr. Goldkind.

DR. WOOD: I find myself feeling a bit uncomfortable with this notion that there is going to be a global chronic pain analgesic. I think it goes against everything we know and everything that we are beginning to understand, and I think that is exactly what your comment relates to.

So, which four different indications would

you need in order to make sure that it was global? How many neuropathic pain and how many musculoskeletal pain, what is the balance that one would feel comfortable with, that would encompass all forms of chronic pain that crossed all mechanisms?

I don't think we have a consensus on that. I think that if one were careful in selecting four indications that were predominantly musculoskeletal, that would leave you with a situation where you may have a drug with an indication for chronic pain that would still not work in many patients who have postherpetic neuralgia or diabetic neuropathy or radicular pain.

DR. FIRESTEIN: Well, the FDA would have to think very carefully about how one would choose those particular indications, it seems to me.

You were going to make a comment.

DR. GOLDKIND: In response to Dr. Wood's comment, our current reality is that we are approving drugs as analgesics, and there is an assumed generalizability, and that is part of why we wanted to discuss this, but we do see drugs that have dental pain and maybe one particular post-op setting that form the pivotal basis for approval.

They are marketed as analgesics and even if we describe the particular pain settings or model, depending on semantic difference, in the Clinical Trial Sections, so people know where the evidentiary base came from, it still is an analgesic indication.

This lumping and splitting, we play out all the time, and we do want to optimize that.

DR. FIRESTEIN: But that is precisely why the bar is so high potentially for a true global chronic pain indication.

DR. MAX: I am very sympathetic towards setting such a high bar for general chronic pain claim. That is the part of Lee's proposal that I love, and I think it is because of this syllogism.

When I talk to company marketing people, they say we would really like a chronic pain claim, or even if it is neuropathic pain, a generalized neuropathic pain claim, because we can send our marketing people and our detail men and sell more drug, and have higher profits, and I think the logic is that incentive would lead to many more trials and from multiple trials, multiple trials in many different disease conditions are the best way to advance the science, and I think that is a great

way to go about things, so we will be able to generalize even better later on.

The missing piece of data, however, is I have asked whenever I have had those conversations, I have asked the marketing person, industry, is there any evidence how much a general claim is worth, why it makes a difference, do you need it for the managed care organization or the pharmacy to pay for it, et cetera, and I haven't encountered any rigorous data or modeling, so let me ask anybody from the committee or agency, would we be better served if there were some economic model or data, if that is partly underneath the reason for going for this high bar.

DR. McLESKEY: I won't respond in any detail, but I would say there is a general understanding that the bar to the claim largely, the likelihood is the larger the market will be.

DR. ABRAMSON: I just want to pick up on Dr. Woolf's comment that a general global approval, if we lower the bar for individual approvals is going counterintuitive to the notion that we are funding their differences among the different pain syndromes, and I think the concept of general chronic pain, I think we have to be very careful

about given this morning's discussion.

I would argue that even if a broad indication was met because you had three indications in these separate areas, that we shouldn't lower the bar in any of those individual indications by the numbers of studies that you would need to show that your drug worked in neuropathic pain, fibromyalgia, low back pain, whatever it is.

So, my concern about having one study in four different areas is that you are diluting the individual iterative process and that everything should be able to stand alone as an indication in that area, and if you hit three or four, you have a global marketing advantage, but you haven't diluted the process for any area.

I think the word "counterintuitive" becomes very critical that we separate all these different pains as much as we can as we better understand them.

DR. FIRESTEIN: Dr. Katz.

DR. KATZ: I wonder if it might be useful to use the opioids as a model to do a thought experiment with the idea of a chronic pain indication. Barring the issues that I mentioned

earlier about addiction and tolerance, and all that, we know that there are clinical trials supporting efficacy of opioids in neuropathic pain, musculoskeletal pain, there are a bunch of different studies, headache, short-term studies even if we want to go that far, cancer pain certainly, does anybody feel that opioids would not meet anyone's threshold to be a general analgesic for chronic pain?

Now, granted, they don't work for every kind of pain. Probably they are not effective for central pain, I would guess, but does a medication have to be effective for every single kind of pain in order to be considered generally to have broad applicability, just as a medication for hypertension might not work for every single patient or subtype of hypertension, but still might have broad applicability within hypertension?

It seems to me that the opioids are a broad spectrum analgesic. Why, therefore, is it not possible that another medication could be a broad spectrum analgesic?

DR. WOOD: Let me just respond. I think one thing that we were talking about over here is there seems to be the impression that 30 percent is

a bad response rate. That is about the average you get in every trial of almost any indication. It is 40 percent for anti-hypertensives, it is lower for antidepressants.

I mean 40 percent is about the rate of response you get to a single drug in the pivotal trials which are submitted to the Agency, less than that for some. So, 30 percent ain't so bad, and if it's 33 percent, so expecting that we will see substantially more than that seems to me to be counter to what we have seen with almost every other drug class we have approved.

DR. FIRESTEIN: Dr. Borenstein will get the last comment from the committee today.

DR. BORENSTEIN: One of the points I wanted to be sure about from the clinical situation is when the drug is approved for a general pain indication or is used in one area, it does get used in another to see if it works.

That ends up being what happens in the clinical situation. I think what it is for the Agency is to decide whether three out of four at a certain level, and pretty good on another is close enough, or is it really great on two and okay on two others, is that good enough.

What you see in patients is whether they respond or not. In individuals, it is really yes or no, do they get an effect and can they tolerate it. So, I think the question for the group is what is adequate to allow a drug to have this indication to allow it to be used in the general public for a variety of pain syndromes that will allow patients to get better and at the same time, use it reasonably safe.

That is what I think the group has to decide, whether that is three or four, certainly the Agency has a better idea of what that truly means. In the clinical situation, I see a patient where if I have a drug where I think it might be helpful, I am going to try it. At some time, I am going to be smart enough to figure out the mechanism by why it works, but sometimes you just have to try.

DR. FIRESTEIN: Before I adjourn, I did want to see if there is any of the officers from 170 that had any additional comments. No? Okay.

Thank you very much, everybody. It has been an exciting day and we have more in store for tomorrow. Thank you.

[Whereupon the proceedings were recessed

at 4:45 p.m., to reconvene on Tuesday, July 30, 2002, at 8:00 a.m.]

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