Two of the other cases were very, very complicated -- the lady with multiple adhesions. So, I think we should not be counting all these patients indiscriminately as complications of constipation.

DR. HANAUER: Thank you. Yes, Dr. Siegel?

DR. SIEGEL: I don't know if I am getting this point correctly, but to me, I don't think it matters too much whether all of those patients were specifically related to the drug in a causal factor. I think that, especially once it becomes a little bit looser in terms of the prescribing, it is important to have some sort of a benchmark so that we can see that when patients who aren't necessarily the perfect patients for these drugs are receiving it, whether we can see, you know, how constipation and those serious complications change when those kind of practice patterns are established.

DR. HANAUER: Yes?

MR. HAMMES: Obviously, the rate of serious complications that we are seeing enough were enough to set off some flags. I would like to think that the efforts of today are going to decrease that rate. So, I would say let's start where we are and monitor it, and if it goes up from here we have a real problem, and it should go down.

DR. HANAUER: Any other goals that the committee would like to address?

DR. KENT: I have a question.

DR. HANAUER: Yes?

DR. KENT: That leads into something you said before that I think is very important. You made the comment before, Dr. Hanauer, that the FDA shouldn't be practicing medicine, and the risk-benefit should be judged in patients for whom the drug is indicated. So, if we are getting complications of constipation because someone with a stricture is put on the drug, what does that mean? What is your view of what that means for the drug?

DR. HANAUER: Well, that means that my view of the risk management is that we have to compare the risk to patients in whom it is indicated compared to those who have complications outside of it. That was the point that I personally made to the agency before.

DR. KENT: But what is the rate we are trying to decrease?

DR. HANAUER: Of complications. Well, we saw some of the complications in clinical trials and we saw some outside of them. So, I think that your question is what we are all grappling with.

DR. KENT: Okay. Just one comment, very brief, on ischemic colitis, and that is the whole discussion and the whole aura around ischemic colitis is as if it is an extremely rare event and this is very unusual. But what the

data are beginning to show is that ischemic colitis actually occurs relatively frequently. We have a huge program of epidemiologic studies to try and get that rate, and it is not 100 percent sure that Lotronex is actually causing all of these cases, but we do take your comments.

DR. HANAUER: We understand that.

DR. LAINE: There were zero in the placebo group. So.

DR. GURWITZ: I think it is challenging to stipulate benchmarks without knowing the prevalence of the condition in the population and the level of use, and 1/1000 may be acceptable under some circumstances but if used among millions of people, then it is potentially unacceptable, and unless we know that, that is an issue.

DR. WEISS: I want to take some disagreement with the fact that we should only look at those who are properly prescribed the drug in the risk-benefit equation. I think we have to look at all the people that are prescribed the drug whether or not it is for the indication when we think about the risk-benefits.

DR. KRAMER: I want to second that. That, in essence, is a reformation of what I said a little bit earlier. In my opinion, if the overwhelming majority of people who get the drug get it inappropriately because of a misdiagnosis, or whatever, and therefore, the overwhelming

majority of consequences is in people who didn't need to be on the drug in the first place, that represents a failure of risk management. I think we ought to take a look at it as risk management, not just what happens in people who have a perfectly accurate diagnosis and have a complication.

DR. WELTON: Especially in a disease process that is so hard to really diagnose.

DR. HANAUER: Thank you.

DR. AVORN: I have another goal of risk management, in response to you question, and that is that I want to come back to the concept of risk in the absence of benefit. I wonder whether there ought to be a way of thinking about the labeling that would encourage doctors to reassess patients after ten weeks of therapy and systematically study whether or not the patient is benefiting, perhaps by a temporary cessation of therapy, and see if the patient continues as well as they were or deteriorates. I think that is a small price to pay for the possibility of getting a lot of patients who may not be benefiting from the drug off the drug. I realize that is not Glaxo's favorite concept, but in terms of not wanting to expose people to any risk if they are not getting a benefit, perhaps there ought to be a protocol that is recommended after twelve weeks, which after all is the main amount of time for which there is data, saying there ought to be a

drug holiday and reassess X weeks after that.

DR. HANAUER: Along those lines, yesterday we recommended a maintenance trial for another drug. You guys have a maintenance trial going on, a longer than three-month trial?

DR. MANGEL: We have a 12-month efficacy study of which we will have the results at the end of July.

DR. HANAUER: Thank you. Dr. Welton?

DR. WELTON: The problem with the drug holiday -- correct me if I am wrong, but I thought your graph showed that the patients all had return of their symptoms with withdrawal of placebo and drug.

DR. AVORN: That was average; it wasn't all.

DR. WELTON: Average, okay.

DR. HANAUER: Any other goals for risk management that we would like to inform the agency of?

DR. HOUN: I have a question on death in terms of a goal.

DR. HANAUER: Death? That is not a goal.

[Laughter]

Should we be looking at deaths?

DR. LAINE: You should always look at death. It is obviously the most objective outcome. I would obviously look at it, I am not sure that I would include it. The likelihood of showing difference in death, it seems to me,

at this time, even in the studies mentioned, is extremely small.

DR. HANAUER: We are not worried about dying in a composite.

DR. BLUM: Unless it is something to do with bowel disease -- a perforation etc., something of that nature.

DR. HOUN: That is what the question was in terms of the complications now show, you know, colectomy, toxic megacolon, perforation. In the future, it is reasonable to assume there will be a death report or more coming in, and I wanted to just make sure that that was discussed here so that when that report does come in the future we have some of your guidance.

DR. HANAUER: I think we are going to have to see the deaths within the context. If we see death of a 20-year old with diarrhea predominant irritable bowel from an ischemic event that didn't have any other predisposing factors, versus a 75-year old with diverticulitis who has a diverticular abscess, it is going to impact us differently.

DR. WELTON: You are more likely to see it with the constipation patient, not with the ischemic colitis patient.

DR. WEISS: But I definitely think you need to monitor the complications and the outcomes of the people that do have those conditions because I think that is going

to be very important.

DR. HANAUER: That is the next question. The drug was released in February. When is the next time point when the agency should be looking at that? The company tells us that they should have some data by the end of this year regarding some of their trials. Is that satisfactory? Do we need it sooner? Later? We are happy with the end of this year.

Anything else, Dr. Houn, on that first category? We can move on? Okay, now we are talking about what interventions in the risk management program should be undertaken regarding Lotronex. Please discuss which risk management tools should be used to reduce the risk and to achieve the desired goals and outcomes. As outlined, various tools -- we have discussed today various potential tools that are not limited to but include changes in the product labeling including boxed warnings, special education programs, the potential of a medication guide, and the epidemiologic studies that have been discussed by the sponsor, and potential studies that could also be done by the agency, and limiting distribution of Lotronex to certain patients or physicians.

I think what we will do is take these one at a time for discussion. The first, since it is probably the most important to everybody, is the issue of labeling and

whether boxed warnings are necessary at this point. We have heard from the sponsor, for a variety of reasons, that they don't think it is necessary but certainly now it is time for the committee to discuss whether the committee feels a boxed warning is necessary. Let's hear discussions regarding that. Dr. Wolfe, you already preceded this with comments. Do you have anything further to add about a box?

DR. WOLFE: I do have one comment. Again, I am not advocating it necessarily, I am just saying it is written down as a consideration. The other aspect that was mentioned I really disagree with is looking at past drugs. Past performance is not necessarily an indication of what we should do in the future. We had a drug recently that didn't have a proper warning and obviously everyone wants to prevent that from occurring again. I don't think anybody disagrees that some kind of warning is necessary to make sure this doesn't actually become a problem.

DR. HANAUER: The other options along the labeling that we have heard are increased warnings or highlighting of the warnings, etc. Dr. Kramer, do you have a comment?

DR. KRAMER: Well, I will tell you why I lean toward a boxed warning. I learned quite a bit this morning. One of the things I learned from listening to the very poignant stories who suffer with the problem is that there is a sense that even their physicians don't have all the

appropriate information to really help them benefit but also prevent their suffering from the treatment itself. So, I am looking for multiple avenues to educate both the sufferer and the physician who is trying to help them, and one of the primary avenues that hasn't been pursued yet is the boxed warning.

That is the reason I asked specifically this morning what is the downside, in terms of educating the professional public, to having a boxed warning. Although I recognize it is not an attractive thing to a pharmaceutical company, I didn't hear a specific downside as part of an educational program.

DR. HANAUER: I am going to bring the boxed warning to a vote unless there is any other discussion around it. I presume that you guys want an opinion on labeling issues.

DR. HOUN: Well, this committee is not really charged with voting because most of the people are guests here. So, what we wanted to have was a brainstorming session, and I suggest that if you did want people to talk about advantages or disadvantages of boxed and you want to bring out people who haven't said things, you can do that.

DR. HANAUER: So, we don't have to vote on any of this?

DR. HOUN: You don't have to vote.

DR. HANAUER: Do you want us to? Do you want a sense of the committee?

DR. HOUN: A sense is fine.

DR. HAVLIK: I was impressed, actually, that the company had at least gone half the way to a box because, if I interpreted their revision of the labeling, they have it in bold as number one warning that constipation is the thing to worry about. I am not in practice so it is easy for me what I think I would do, but that would certainly get my attention.

From the drug company's side, it would seem right now that as much preventive medicine that could be exercised that would not undercut the ability to promote the drug is to the company's advantage. So, I am kind of caught between saying that what I see in the labeling is pretty good versus not really now knowing whether the physicians are going to respond adequately to that. In fact, I had a discussion with a practicing internist who gets bombarded. I won't speak for him but I had the feeling like even a warning might not be enough to get his attention.

DR. HANAUER: Well, let's take it right to the proposed labeling and asked for discussions off of that.

DR. HOMBOE: I just want to comment briefly. I am the general internist being referred to, but if you look at the data -- and I think we also heard some this morning, the

printed materials, whether it be a box or a "dear healthcare provider" letter, don't necessarily work very well. We have seen that in other areas of medicine, including guidelines which are not followed. So, regardless whether you use the black box, I think at a minimum you are going to have to highlight the things you are most concerned about, whether it be a black box, medication guide etc., but you are going to have to take it another step. I honestly don't believe that publishing the stuff and putting it in as inserts is going to be enough. I think it is really going to have to be part of the education program that has been talked about.

DR. HANAUER: Well, we agree. We have heard that irritable bowel is a multi-component disease and that risk management is a multi-component attempt at solution, and everything we are going to talk about is assuming other things.

DR. WOLFE: One point that was alluded to before was the role of the drug rep. I think you have a program in place, and I think that is very laudable and very important because a lot of physicians get their information from the rep. They have to pass a test to make sure they know -- they have to really tell physicians to prescribe this drug appropriately.

DR. HANAUER: Let's just go to the label and get some comments on this. Indications and usages -- is this

okay, or do you want to modify it or what do you want to do?

DR. HOUN: It is fine to get suggestions.

DR. HANAUER: You are not thrilled with it.

DR. HOUN: The concepts. Don't edit the words, but the concepts.

DR. HANAUER: Got that charge? So, the indications -- Lotronex is indicated for the treatment of women --

DR. LAINE: Where are we?

DR. HANAUER: We are on page five of the draft. Lotronex is indicated for the treatment of women with diarrhea-predominant irritable bowel syndrome. Diarrhea-predominant IBS is characterized by at least three months of recurrent or continuous symptoms of abdominal pain or discomfort and diarrhea with either urgency and/or an increase in frequency. See appendix, and the appendix describes the wrong criteria that support diagnosis of diarrhea-predominant irritable bowel syndrome, abnormal stool frequency, greater than three bowel movements per day; abnormal stool form, loose or watery; and abnormal stool passage, urgency or feeling of incomplete evacuation. So, without talking about the words --

DR. LAINE: It is interesting because the indications say three months of basically pain and diarrhea. You know, diagnostic criteria talk about any 12 weeks within

the last one year. I am not saying that they are absolutely exclusive but one is stronger, if you will, in terms of talking about diarrhea predominant right in the recent past, while the other one could be read as six months ago, you know, somebody had diarrhea and it is resolved now.

DR. KENT: We put it as it is because we felt it was stronger the way it is.

DR. LAINE: I like it better in the indications is what I am saying.

DR. HANAUER: The next are the contraindications, which are patients with a history of chronic or severe constipation or sequelae from constipation; history of intestinal obstruction and/or stricture, toxic megacolon, perforation or adhesions; a history of ischemic colitis; or known hypersensitivity. In addition, should not be initiated in patients experiencing constipation which they describe as less than three bowel movements per week, and/or hard or lumpy stools and/or straining during a bowel movement.

DR. LAINE: Now we are in the recent past, for instance -- in other words, those who had it three weeks ago, I wouldn't include them, as an example, something along those lines.

DR. WOLFE: What about alternators, people who have constipation alternating with diarrhea?

DR. HANAUER: Is that a contraindication? Is alternating diarrhea and constipation a contraindication?

DR. LAINE: What I was trying to say is if they had constipation fairly recently it would be, but if they had it six or eight months ago -- I mean, I am making broad statements, but if they had it a couple of weeks ago, it would be; if they had it months and months ago, it wouldn't be. Again, I am not sure that is based on great evidence but that is what I would maybe suggest to handle that a little.

MR. LEVIN: Is there another way to deal with that? Going back to the indications and usage, we said the safety and effective has not been established in men. Should something be said -- the safety and effective has not been established for alternating diarrhea? I don't know why we just pick men. What about all the other conditions?

DR. HANAUER: I think that is a very good point. Thank you. Warnings -- gee, I really don't want to read this whole thing. It is on the bottom of page six --

DR. SURAWICZ: We have read it; it is good.

DR. RACZKOWSKI: Dr. Hanauer, one of the issues that has come up in the contraindications section is the notion of severe constipation as opposed to mild and moderate constipation, and the definition of severe constipation being a subjective one. I wonder if the

committee could just give some input about their comfort level with use of that sort of terminology. Is it specific enough or is it satisfactory?

DR. HANAUER: Well, my view is that at the top of the contraindications they mentioned a history of chronic or severe constipation. The lower part -- maybe it should be moved up, which is a small point, but it shouldn't be given in anybody with current constipation.

DR. SURAWICZ: And you also have the four days.

DR. HANAUER: Which is less defined.

DR. SURAWICZ: You also have if it doesn't resolve within four days, which is another way that people can measure whether they would fit into the severe constipation group.

DR. HANAUER: I mean, the smart way would be to move it closer together because we have heard that we want simplicity for people.

DR. LAINE: And, I think that definition is acceptable that they have.

DR. RACZKOWSKI: In our discussions with the company, I think one of the main points that has come out is that severe constipation, as intended here and the company can correct me if I am wrong, but it is intended not to be assessed by any objective criteria but by the subjective presentation of the patient saying that he or she -- in this

case she has severe constipation, just like if you have a severe migraine or a mild to moderate migraine.

DR. LAINE: But, they now define it here. So, as Steve says, if you move this up there is a definition of constipation here.

DR. HANAUER: Frankly, we don't know how to define severe constipation. It is a subjective condition unless it has a complication.

DR. WELTON: I think that is his point. Then it should be just constipation, not severe constipation.

DR. HANAUER: No, we are talking about the contraindications now, with a history of severe constipation or current constipation.

DR. WELTON: But what I am saying is that he is suggesting that we should drop the modifier "severe" and just say with a history of constipation.

DR. HANAUER: So, anyone who was constipated 20 years ago shouldn't be contraindicated.

DR. WELTON: That is what his question is, his question is do we know what we are saying, especially in surgery.

DR. HANAUER: The next is sort of no-brainer stuff to us. Special education programs -- any comments from the committee? First of all, I will give my personal view that I thought that what I heard from the sponsor was really an

outstanding conglomerate of a risk management program from your standpoint. I thought it encompassed a lot of things that we were prompted on coming into the meeting, and incorporated both education to the patients and to the physicians. The key, I guess, that we want to know is that you follow through with that, and that we are being able to monitor that effect along the way. Any other comments regarding the education program that we heard about? Additions?

DR. SURAWICZ: Yes, I disagree with you that it is a no-brainer. I think that maybe this is where we could focus a few minutes with brain-storming because, while I like the program that they have, I would like to see them go a step or two beyond and do something that is really new and different, that provides the education to patients directly. They could work with Nancy Norton's foundation. They could work with specialty societies. There are a lot of ways.

I think if it is really going to succeed it has to be something different than what we already found worked five percent of the time or didn't work at all. So, educational materials addressed to patients that would be written at a grade five level -- really, really simple; lots of people will understand it; use of visuals, cartoons. Not just translating into languages but really making it as simple and consumer oriented as possible. If you look at

not drug advertising but the rest of advertising, it is really, really effective. Maybe building teams with advertising agencies that know how to get to the entire population.

In one of these books that I read, and I can't remember which one, there was a list of the specialty societies that are part of a drug complication reporting system. What I noticed in that list of all of the specialty societies was that none of the four GI societies are in that list at all, and that was a real surprise to me, that all these other societies have gotten together to do some sort of reporting of complications. That is not specific to this drug or this company, but something that we might want to look at sometime in the future.

So, I would like to see really innovative ways of directing education to physicians, all physicians but especially GI docs, and your primary care docs. Those are your two hugest markets. And, then directly to patients. And, something different. I mean, the examples in the book, to me, of the patient education material -- I think there were five or six examples, and there was one that looked to me, if I were a patient, that I would read. The rest were tiny little types that looked exactly like what I don't read as a doctor and would read even less as a patient.

DR. HANAUER: I agree. It is a real brainer.

That is why she is going to be the next chairman here.

DR. LAINE: And to follow up on a point too, since fortunately or unfortunately a lot of doctors get their information on drugs from representatives, I mean one of the things that the companies do extremely well is monitor drug web visits, to which doctors and what drug they were there for. Although that doesn't tell you how effective it is, one of the quantitative things, I guess, the FDA could get from the company is really having the company commit to X number of visits per physician or per area to discuss this particular drug with these particular educational tools, and just to monitor that and just to make sure that they really are, indeed, following up with educational programs to doctors, or educational material.

DR. WOLFE: Regarding educational material, also there are new avenues. You mentioned websites. Websites can be made to have warnings flashing so people can actually see them, consumers and physicians. As far as physician education, I think I can safely assume that all of us here do give lectures that are occasionally sponsored and we are given freedom to say what we want to say. On the other hand, this is something I think should be mandated for physicians who will be speaking on irritable bowel syndrome. If they mention drug therapy, they should mention contraindications during their lectures.

The other thing is that there are certain avenues -- Chris mentioned new ways of doing education. One way, for example, is computer programs with different case scenarios for people with certain conditions and how they should treat them, and the kind of patient who would not get that kind of drug. So, there are ways to reenforce the idea of when the drug is appropriately used and when it is not appropriately used.

MR. LEVIN: I just want to reemphasize the comments about the Internet because that is really where people are going to get it, and already a tremendous number of people are getting information from the Internet. I know a lot of people don't have access to the Internet yet but if we are looking ten years down the road, that is really where the information is.

Imagine my surprise when I dialed up web MD and on their home page, in the left-hand banner is an IBS Glaxo Wellcome connection and you go right to their URL, and it has information but it is also going to tell you about a new product that is available for treating IBS. So, I am concerned that there is a lot of push electronically, and I am not sure that what people can dial up necessarily reflects the discussion we are having today about some of our concerns. For example, if you go on to medscape, which is another of the major websites, and you go to the drug

information patient handout for alosetron, it is a very mild-manner statement of the risks. So, I think we have to be aware --

DR. HANAUER: Why don't you read it to us, if it is brief?

MR. LEVIN: Sure. First of all, it says, important note -- this is intended to supplement, not substitute, for your doctor. It is a one-pager, and under side effects it is constipation, headache, or stomach upset may occur. If these effects persist or worsen, notify your doctor promptly. If constipation occurs, it may only be temporary. If it occurs, your doctor may recommend ... and on, and on. I mean, I think it is a very mild-mannered presentation of the kind of potential severe risks that we are hearing about today.

So, how to deal with the information revolution and to make sure that the data that many, many millions of people are dialing up is accurate and presents risk I think is a critical issue.

DR. HANAUER: We understand that.

DR. KENT: That is based on the original label.

[Laughter]

DR. HANAUER: We are not holding you to proactive standards yet.

MR. HAMMES: I want to reemphasize here the role

of the pharmacist in all of this, and to include the pharmacist in this education process. They are the person that is going to see this patient most frequently. They are the professional that is likely to be selling them their laxatives and, if they are any good, they will pick up on a problem -- if they are selling an OTC that is related to this, and it is a good way to get the information into the patient's hands. So, you have to include the education of the pharmacist first off, and I am really intrigued by this medication guide thing. I think you need to force the less than perfect pharmacist to get involved in this. I was very disillusioned with our young lady who told us she didn't get any information because she got mail order. I mean, we need to do something about that.

DR. HANAUER: I guess that brings us to medication guides, and we are not taking a vote but are there opinions from the committee members?

DR. BLUM: I would like to say one thing about the pharmacists also. The pharmacists are usually in the community, and if you mention language barriers and being able to educate, the pharmacist in a foreign-speaking community usually speaks the language of that community to communicate with the individual. So, they would be the best -- better than any type of print media -- to get the information across. But the pharmacist also has access not

only to the OTCs but the herbals that they may be taking, which could interact with all of this.

MR. LEVIN: As a veteran of the med guide wars over the this last decade, I would like to strongly urge that the FDA think very seriously about requiring a medication guide for this product. I think medication guides, which establish standards for presentation and content, and format and the graphics are really important, and I think the most important facet is that it requires that risk information be up front rather than buried somewhere down the line. Even though we have this limited approach to medication guides, I think this is a wonderful opportunity to use the medication guide regulation as a public health protection measure.

DR. HANAUER: How would you assess that then? How would you suggest that they assess the benefit if they imposed a medication guide?

MR. LEVIN: I mean, you would have to have some control to compare it --

DR. HANAUER: So, would you suggest a study of a medication guide in one population versus another to test it in one managed care group or another?

MR. LEVIN: I am not sure that is how the regulation authorizes medication guides to be used. The regulation that is currently there, from '98, I think says

that you can select up to five to ten drugs and then require that a medication guide be provided by the manufacturer and must be dispensed with that drug. So, I don't know if you can parse that into specific populations. I don't think I would suggest we need to study medication guides yet again. We have been there; done that. After all these years of comments and actions by Congress and the agency, comments by everybody, the decision was that where drugs present a certain level of risk it is appropriate to have a medication guide.

DR. HOUN: What would be useful in a medication guide intervention evaluation would be to do an audit of pharmacies to see if that is actually happening. Even though regulation means that there is force of law to require this, there is force of law to require you to drive 55 miles an hour or less and, you know, whether people do it or not or whether pharmacists do it or not, that could be checked on.

DR. HANAUER: Do we have data that these guides make an impact?

DR. MORRIS: My name is Louis Morris. I am a consultant for Glaxo, but I am also one of the veterans of the medication guide wars. I worked at FDA and was responsible for heading up that project. Just in terms of some of these questions, just a couple of comments.

The first is, as you might guess, there is no guarantee that requiring it by FDA regulation actually results in the distribution of information. As Dr. Ostrove mentioned, there have been studies done, pharmacy shopping studies, where people went in, filled prescriptions for the estrogen patient package insert, which is required by a specific regulation, and somewhere between 20-40 percent of people received that document.

On the other hand, there is some evidence that changing the packaging is a more effective solution, and one of the things that Glaxo did not go into detail over that is significant to this discussion is that in the proposed new patient package insert there has been a significant change in how that would be packaged. The current insert is attached in a perforated sheet with the physician insert. The pharmacist has to pull out the physician insert, tear off the patient package insert and hand it to the patient. In the current plan, the patient package insert will be a separate document. It will be attached to the bottle itself.

One of the things that we know from the new work that is being done on systems and systems approach to preventing medication errors is that the best solution is the one that fits most easily into the routine practice of whoever is distributing it. In this case, what we have is a

pharmacist who simply has to pull the bottle down off a shelf. The bottle for Lotronex, the average size is 60, which is a month's supply, and the majority of prescriptions are at that rate. So, all the pharmacist has to do is take the bottle off and put it in the bag. The pharmacist doesn't have to do anything special to distribute the medication guide. It is actually attached to the bottle. So, I think that packaging solution goes a long way in terms of concerns about getting it distributed, and I think historically packaging solutions have been more effective than regulatory solutions that simply require it.

The second point I wanted to make about medication guides is that one of the downsides of a medication guide is that there is a standard format, and that if a medication guide is required, then the company would be required to follow the standardized format. Currently, the company has plans to thoroughly test the information to make sure the message is getting across, and having the flexibility to actually get the message right is one of the concerns that I would have where, if it is a medication guide, it has to be in the standardized format.

MR. LEVIN: Lou, I think that is the argument that is always used with any standard or guideline. When guidelines are issued, people say, well, medicine is an art; it is not a science, and you can't stifle innovation. So,

there is always a tension between those two sides, and I think we have to recognize that but one doesn't preclude the other.

I think the standardization is important because when people go in an survey, even today, the accuracy and completeness of the voluntary medication guides that are available in pharmacies there is a lot of important stuff that is left out. So, at some point in time you have to develop a standard for what is to be included in a medication guide and how it is to be evaluated. I think we have done that ad nauseam since 1995 with medication guides with all the permutations, with all the parties -- two years of the Keystone process which I was part of with all the players at the table, and I don't think we should continue to debate whether there is a reason to try to have a standard medication guide. Whether it is appropriate or not for this particular drug I think is the issue that we are concerned with today.

DR. HANAUER: Go ahead.

DR. OSTROVE: Can I just had one additional point concerning the standardization issue? Dr. Levin is right, there has been a large history with this. But, I think it is important to recognize that the regulation permits exemptions and deferrals and that if, in fact, the manufacturer has data and is doing research on what best

communicates to a particular patient population that shows that a slightly different format would work better for that population, that certainly is something that we would take into account in looking at it. The standardized format is one that we feel is good because that way people can look in particular sections to find out where the particular information is that they are looking for. However, if there is data, then that is something that we will always take into account, and we will not be overly restrictive in determining what is absolutely necessary under those circumstances.

DR. AVORN: There are well established approaches, very well known to industry when one wants to sell a product about how do you get information out, how do you make sure the message got through, is it working and if it isn't working how do we change it to make sure that it works. That is fine. I think it is just time to put those well-established approaches also at the service of getting information to doctors and patients about problems with the drug, and that is completely within the purview of what companies know how to do and I think we should expect that they will do it. When we have a drug that is on the market we don't say it makes as a drug, let's just give it to people and not see if it works. We demand that we know whether the intervention is working and I think we need to

do the same thing with informational interventions.

DR. FISHER: Hi. I am Rosemary Fisher. I am actually here as a consultant for Glaxo. I have a concern, as Dr. Blum did, about the mail order prescriptions and things getting across. I actually wonder whether the attached tear-off on the bottle, 60-pill medication instruction sheet as opposed to a medication guide would be a more guaranteed was of known that in the mail order prescription that would be getting to the patient because it was attached to the bottle, and not having to have somebody who is just throwing things in a box, making sure that a medication guide got in there.

DR. WEISS: I am definitely leaning toward the medication guide, and it is something that the company reps. had mentioned, that this condition is really something that the patient goes to the doctor for, and it is the patient that has to recognize whether or not they have constipation and seek treatment for it. And, I think that is the kind of thing that we really need to have in a medication guide, educating the patients, more than the doctors, to seek treatment. So, I can see that that is another way to do that.

DR. HOUN: The med. guide could be attached to the bottle, just as the PPI.

MR. HAMMES: And why can't we do both?

DR. HANAUER: It sounds like we are doing everything -- to them.

DR. HOUN: So, I guess the consensus is that people are recommending a medication guide.

DR. HANAUER: Not necessarily. I think that we are hearing a composite effect that Glaxo Wellcome has told us that they are doing, and I am not certain that adding everything that you can do up front now is going to be better, worse or -- my recommendation is to look at a variety of different means to assess this. You are asking for risk management which means studying it and imposing all these things at once, you are not going to know which is the best way of making an impact right now.

I certainly agree also with Dr. Surawicz that the organization would like to take part -- the American Gastroenterologic Association, the ACG, and the functional research group should also get involved with assessments and education as well.

DR. SURAWICZ: I would give the company the freedom to come up with something better than a med. guide. If we don't mandate what they do, maybe they will come up with something really creative and better that will set a standard for the other companies when this comes up next time.

DR. HANAUER: I would like to see some studies out

of it, which is what you are proposing. You can't assess it unless you are evaluating it in some controlled manner -- different modalities.

DR. KRAMER: I do have a little bit of a concern about a strategy in risk management which would test one by one by one single interventions, and this where it may come in handy to talk to a communications researcher or a psychosocial researcher. My understanding of the field is that, much like where often one drug at a time isn't the way to treat the whole disease, you need multiple approaches, multiple avenues. So, that issue may already have been sufficiently studied in communications research so that we know that we should expect poor increments with a single intervention, one at a time.

DR. BLUM: Just one question on the med. guidelines, does that include the Med Watch number, the telephone number for patients to report or anyone else to report in the med. guide, and should that even be considered as a way of gathering data?

DR. OSTROVE: The regulation doesn't include that. It certainly could be included. That is something that we are looking at for other regulations having to do with professional labeling at this point.

DR. HANAUER: Besides what we have discussed, does anyone around the table have ideas or opinions as to how

they could improve the benefit side of the drug? We have talked a lot today about the risk.

DR. WOLFE: Just one last idea, there is a consumer magazine in which patients could actually write their own stories. I think that is one way of approaching it. They can actually state what the disease is and what benefit they have from it, from the different treatments.

DR. HANAUER: Anything on the up-side? How can we improve the efficacy? Any specific opinions? I think you have heard that the education is to try and limit the use to the indicated population where we have seen benefit.

DR. BLUM: That is the best way because if you don't give it to the right population you are only going to get the downside and it is going to give it a bad rep.

DR. HANAUER: Any guidance from the committee on what is the best way to evaluate these interventions? I think, again, we have heard a number of proposed studies from the company. There is a whole variety of different controlled and uncontrolled studies. Anything in addition or preference from the committee members or our consultants? Yes, Dr. Welton?

DR. WELTON: When you asked me earlier whether I had any suggestions about what else to look at, it occurs to me, and I don't know how to do this because I have my own area of expertise which is very limited, but it occurs to me

that although you may not see vasospasm in some of these studies, you may have a relative ischemia of the mucosa because the studies that were presented back in November suggested that increased uptake of water and increased cellular activity you could have a fixed inflow with a hypermetabolic state, leading to relative ischemia of the mucosa. I can't tell you how to study that particularly in a mouse or a rate model. I have a concern about the PET scans. As far as I know, that doesn't work because there is too much background information, but there may be a way to look at mucosal ischemia and relative hypoperfusion from metabolic activity.

DR. HANAUER: Dr. Houn, any other aspects regarding evaluation? It is a very open, broad-based question for us.

DR. HOUN: I think one is to reaffirm that interventions that we do institute, you are looking to have us and the company evaluate that effect. That is a new step for FDA because we don't traditionally evaluate a labeling change or an intervention. So, I think the fact that you are expecting to happen is something that I want to reaffirm.

DR. HANAUER: Speaking for myself as a member of the committee, I think that that would be one of the better ways, and it certainly would be useful to have an

independent demonstration of an effect. You are going to hear about a series of interventions and studies from the company but I think that as long as you are using this as a model, and no drug wants to be a model, I am sure, it would be useful if you developed your own tools to assess and validate what you are hearing from the other side.

DR. HOUN: So, one thing I would like to know is if we do undertake an independent evaluation of some of the risk management interventions, I am assuming our labeling will change to outline some of your recommendations for contraindications and for indications, and we could evaluate, either by a chart audit or the automated databases, in fact, is there, like, ten percent or less of patients who are receiving Lotronex having contraindications, conditions, or other medications. We could do that kind of a study, and is that something you would be recommending in terms of appropriate and safe use, that type of an evaluation of practice?

DR. HANAUER: Yes, but I would also urge you to do it by physician specialty because, like in anything else, the specialists are going to try and push the bubble more, probably with more experience in doing that than the primary care physicians. Other comments?

DR. WEISS: I would like to see, if you do a medication guide or package insert, that the patient

actually gets it and that they actually understand it. I think, from what Dr. Rodriguez showed us, that that is probably an important step to take.

DR. AVORN: I think also some survey methodology of both patients and doctors to understand not just what are their behaviors but what they know because you want to know what the doctor is telling the patient in the office about the side effects. Again, I would just turn to the industry and ask how they evaluate how well a direct to consumer advertising campaign is working and use that exact same methodology.

DR. HANAUER: The last point we need to go over is if you don't do what they say, what next. What do you want to know, Dr. Houn?

DR. HOUN: Let's say we do make contraindications for people who have had severe constipation or constipation in the last three weeks -- I mean, those are very defined terms, and we find that, gee, when we do our evaluation 50 percent of patients in this study who had, in fact, contraindications were getting the drug, or we look at adverse event reporting -- right now we have six cases, of which three had constipation, and if we look at the numbers of contraindications on adverse events, are they decreasing? If that doesn't happen and if you could set up some acceptable levels to achieve, and if those levels are not

achieved, what would you recommend? Would you recommend at that time going back for another year doing education? Do you recommend -- shall we reconvene the committee next year to reassess the programs? If we are finding that GI people have less rates of contraindications, should they be the ones that prescribe this drug? So, that is what we want -- we want to push you further. You said all these lofty goals about education, do right, no more, you are going to be better -- how about if it doesn't happen? What should we do next?

DR. HANAUER: Well, my answer is going to be simple. It is just what we are asking of the sponsors. When they come to us with studies and we learn from each study, and we learn what is good and what is bad and then we redesign based on that. I think it is going to be difficult to as that without the specific information that we get out of these maneuvers. Dr. Ferry?

DR. FERRY: Yes, I would like to second that. I mean, this has been difficult enough today --

[Laughter]

-- it may not be that clear-cut, you know, a year down the road either. I think we are going to have to reassess it at the time. I would have a terrible time coming up with some pre-plan that if this doesn't work you have to take some other major step.

DR. SIEGEL: One point on that, I am hearing a lot of tension between, you know, hearing the importance of really being sure that the drug is prescribed correctly to the people for whom it is really indicated and, yet, there may be some groups of physicians who want to push the bubble a little bit and they really know enough to be prescribing it in different ways. I think we have to be very clear up front, if you are looking at that kind of an evaluation down the line, of whether you really did want to hold the line or whether it really was okay to push some of this prescribing a little bit by certain subgroups of physicians or by any physician. I think that the real issue there comes down to tying it to the rates of problems that you are seeing at that point, but it seems to me that if we sit here and say, well, if we find a problem later on, but we haven't actually defined up front whether that is a rigid goal that we have, you are not going to be in a position to say anything different in a year from now.

DR. HANAUER: I don't understand that.

DR. SIEGEL: Let me see if I can clarify it. We have made some points here on how important it is for this drug to be prescribed precisely for those patients for whom it is indicated, that is to say, in terms of, you know, not having a history of constipation and other predisposing risk factors that would potentially give them problems. Yet, if

it is being prescribed -- and the point you made, unless I misunderstood it was that some specialty practices may have a patient who does have a history as an alternator, or something like that, but for whom there is really nothing else, and they are suffering and they are in terrible shape, and they really do want to give this patient a trial on the drug, and then they have a problem. I think that we have a tension there. I mean, we have said that a critical goal for this drug is that it be restricted and prescribed according to --

DR. HANAUER: I think you misunderstood what I was saying, which was that since you are studying it one of the ways to assess is by physician group and within and without the indications. So, we are saying very much the same thing, that we need to evaluate where the complications are coming and where the benefits are coming.

DR. SIEGEL: It may be that we are saying the same thing --

DR. HANAUER: I don't feel tense about it.

DR. SIEGEL: That is good. No, my concern is if you are thinking about what is the next step, it is going to be confusing data a year from now if we haven't reached some of the benchmarks that we were aiming towards, but part of the reason for that is because certain people have really, with great consideration, decided to use the drug in

different ways, and there is no barrier to that happening at this point.

DR. WOLFE: Are you saying that now, for example, 50 percent of the cases were due to people using the drug incorrectly and next year you want it to be 25 percent only? So, that shows an improvement and that the program is working.

DR. HOUN: I can't say that I have thought through exactly what those guidelines will be. I think that we did talk about having a benchmark and looking towards improvement toward that benchmark but, at the same time, I think that there has been no statement here that it should be in any way restricted so that people won't be using it for some patients for whom they think it is particularly indicated, and with an illness like this where people don't have a lot of choices, I think it is very likely that people will push those boundaries.

DR. HANAUER: How else can we advise you?

DR. HOUN: Dr. Wolfe, did you have a question?

DR. WOLFE: Are you looking for guidelines from us?

DR. HOUN: That would be great, if people have some suggestions.

DR. WOLFE: The only way to assess this is looking, I guess, at prescribing practices to see who is

getting the drug but also the complications. I think that is what we are going to be looking at to see if people who had complications were, indeed, inappropriately prescribed the drug. Again, the confounding factor, as has been brought up, is that some people may just want to try anything they possibly could. Maybe in that case a consent form would be necessary.

DR. BLUM: There is one other thing, trying to get physicians in the office but most of these complications are going to occur, especially the constipation -- getting them to report, say, to Med Watch or someone else because that is really your population of under-reporting. It will occur in that population.

DR. AVORN: The web MD interface that Mr. Levin told us about is something which, clearly, the company is eager to take advantage of, and maybe the agency may want to talk with the company about other ways in which that collection of names and addresses, phone numbers and e-mail address which are being assembled can be used for collecting data proactively, as well as for marketing, and I think that could be a very nice tool that could be used for a number of different purposes.

DR. WELTON: Is there a minimum of workup that we are going to say needs to be done when a diagnosis is made -- again, ischemic colitis?

DR. HANAUER: By the physician?

DR. WELTON: If a patient calls in and says they are having some bleeding, does the prescribing physician have to work that up?

DR. HANAUER: That can't be regulated. Do you have a comment?

DR. GURWITZ: Yes, the only thing I just want to reiterate as far as next steps is how important it will be to find out what the patients and providers understand about the educational program. If you see a reduction in complications, then you can say the program is working and that would be okay, without understanding potentially what it was about it that worked but just know that is worked. So, it would be particularly important if you get back here in a year and you find out things aren't better, and if you don't know what the providers and patients understand despite all your databases and stuff you are going to have a hard time deciding what your next steps are going to be because you are not going to know what part of the message they did or did not get.

DR. HANAUER: Okay. I want to thank again the company, Glaxo Wellcome, for their presentations and their willingness to work with us and the committee to try and compact the discussions. I hope we have not influenced in a negative way. I think we squeezed this lemon as much as you

can get out of it today.

I want to thank personally Dr. Talarico for supporting me during my chairmanship here, and Dr. Gallo-Torres, and we look forward to the reign of Dr. Surawicz for the next meetings. Thank you, all. Have a good night.

DR. HOUN: Thank you so much.

[Whereupon, at 3:30 p.m., the proceedings were adjourned.]

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# *CERTIFICATE*

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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