

FDA's Regulatory Armamentarium: Presentation by Anne Trontell (FDA) & Committee Discussion

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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Highlights

THE FDA ARMAMENTARIUM:

- **VOLUNTARY LIMITATION OF MARKETING:** Voluntary limitation of marketing (e.g., no Direct-To-Consumer advertising, restriction to certain specialty groups, restriction to certain specialty journals).
- **LABELING RESTRICTIONS:** Labeling restrictions (e.g., black-box, second-line use, contraindication in certain patient populations).
- **TARGETED EDUCATION:** Targeted education or outreach that goes to doctors and/or patients (e.g., Dear Doctor letters, patient medication guides, other academic detailing that targets prescribers with information about safe use).
- **REMINDER SYSTEMS:** Reminder systems that prompt people on appropriate use (e.g., patient agreements or informed consents where patient acknowledges and accepts risks, attestation by physician that appropriate-use conditions have been met such as is used for Lotronex).
- **DISPENSING RESTRICTIONS:** Limitation of amount dispensed or number of refills.
- **PERFORMANCE-LINKED ACCESS SYSTEMS:** Performance-linked access systems that defines a population of providers or patients to whom access is restricted (e.g., the clozapine patient registry in which patients are required to show proof of an adequate WBC count - "no blood, no drug"; proof that woman is not pregnant before dispensing thalidomide).
- **SUBPART H RESTRICTIONS:** Subpart H can restrict distribution "for drugs that are important and that you could only be satisfied that they were safe for use in that setting". Dr. Temple said that that, to his knowledge, this had not been imposed after approval but "I don't think it is impossible".
- **MANDATED POST-APPROVAL STUDIES:** FDA can mandate new safety studies to address a new safety issue.

DISCUSSION:

- **EFFECTIVENESS OF BLACK-BOX WARNINGS:** Dr. Platt asked how well black-box warnings work, and cited the example of cisapride that was withdrawn after black-box warnings did not work. Dr. Trontell said that the effectiveness of these programs was not well tested, but that in the case of the black-box for ketorolac “there is actually very high conformance”. With Seldane, the black-box for torsades de pointes eliminated about 90% of inappropriate prescribing but not entirely and “there were still unacceptable levels persisting”. “So, it is a mixed picture...”. Dr. Wood cited Rezulin and bromfenac as examples where the black-box did not work but “That is not to say we shouldn't do them...”. Dr. Dworkin asked about different levels of warning. Dr. Trontell said that one can have different levels within the black-box category.
- **MANDATORY ACADEMIC DETAILING:** Dr. Platt asked what “mandatory academic detailing” means with regard to who develops the content, who delivers it, and who oversees compliance. Dr. Trontell said that this system, to her knowledge, is “not in place”.
- **WRITTEN AGREEMENT BY PATIENT MAY NOT INDICATE COMPREHENSION:** Dr. Day pointed out that even though people may “sign a piece of paper we don't know that they really understand until we give them a comprehension test” as has been tried with Accutane. When a survey was voluntary, only 20% of patients filled it out.
- **DTC ADVERTISING WITH BLACK-BOX WARNING:** Dr. D’Agostino asked if there were circumstances where a black-box still permitted Direct-To-Consumer advertising. Dr. Temple said that a black-box makes reminder ads impossible, but it is conceivable that a Direct-To-Consumer advertisement would be acceptable if it conveyed the “black-box in all its full unpleasantness”. Dr. Wood suggested that “restricting DTC should be a separate or additional issue to black-box warnings” and that although FDA cannot mandate a DTC restriction, “it is within the rubric of the commission's recommendations”.
- **DTC BY FDA WITH PDUFA FUNDING:** Dr. Gross suggested that FDA does “direct-to-consumer education from the FDA's point of view, either pairing it with the ad from the pharmaceutical companies, doing it separately”. Dr. Temple said “That takes money beyond what we usually feel we have.” Dr. Gross said “That is why I suggested PDUFA funding”.
- **EDUCATION THROUGH MEDWATCH AND PUBLIC HEALTH ADVISORIES:** Dr. Trontell said that FDA can educate through MedWatch and Public Health advisories.
- **PROMPT NEGOTIATION AND IMPLEMENTATION OF VOLUNTARY RESTRICTIONS:** Mr. Levin asked if a “voluntary” restriction could be “imposed” by FDA because of the threat of removal from the market. Dr. Trontell said that was “a difficult

question” but that “to my knowledge, these agreements that have been put in place relative to marketing have been ones that have been offered by the drug companies”. Generally, in matters of “risk management or risk minimization, there is a back-and-forth process that is directed to the feasibility of actually putting some of these systems into place”. Dr. Wood said it the committee makes “strong recommendations that something should be done, it would be pretty tough not to follow them”. Dr. Morris expressed concern about “the ability of FDA to insist on and enforce conditions which will limit the distribution and use...” but, that said, some risk-management results have been positive (e.g., Lotrinex). However, he is concerned about the time it takes to negotiate with the sponsor, and that “whatever we do recommend today”, it is going to be a “long haul”. Dr. Wood said that the committee should “light a fire under these guys that will provide ammunition to the FDA in their negotiations....”. Dr. Jenkins said “we are committed to making our decision on your recommendations on these applications and these products very quickly after this meeting”. Dr. Wood said “There is nothing beats setting a time line...”.

- **REMOVAL OR RESTRICTED USE OF HIGH DOSE CAPSULES:** Dr. Nissen asked if the marketed doses could be changed (e.g., market the 100 mg celecoxib capsule but not the 200 mg capsule so as to make it difficult for a patient to take the number of capsules required for an 800 mg dose). Dr. Trontell agreed that this could be done. Dr. Jenkins pointed out that an unintended consequence could be that patients might have to pay more for the same number of milligrams. Dr. Wood suggested that one could have different restrictions for the different capsule strengths.
- **NEW POST-MARKETING STUDIES:** Dr. Crawford asked if one could mandate “definitive, well-designed postmarketing surveillance studies”. Dr. Jenkins agreed and said that “postmarketing commitments are not only made at the time of approval, they can also be made after approval when a new issue comes up”. Dr. Wood suggested that “your success in getting these studies completed has not been terrific” but Dr. Jenkins said “the record is much better than it is portrayed often in the media” and that FDA posts information on its website “so you can see if companies are meeting their obligations or if they are falling behind”.

Presentation Text

DR. WOOD: Let's get into our seats and let's begin. I have taken the chair's prerogative to change the program. What I have asked is Dr. Anne Trontell from the FDA to give us a short presentation

on what the FDA's regulatory armamentarium looks like in terms of the potential restrictions or other changes they could make to a drug that might be relevant to this discussion in

order that, as we go through the next question, and subsequent questions, we can do that in the most informed, thoughtful way. Anne has very kindly agreed to do this very quickly--I mean, to prepare it very quickly, not to go through it very quickly. When we finish, I will ask her to stay up there and we will have the opportunity to discuss the various options with her in some detail so that we have got a really good handle on what the various issues are. Anne.

DR. TRONTELL: Thank you. This is a list of some of the options that have been outlined or experienced by the agency. I am going to present them quickly sort of in a rough progression from those that are voluntary and least intrusive to those that are most intrusive.

One option that I will start off by listing is not, in fact, one that is under the agency's purview to require but, certainly, a number of the sponsors have come forth and made voluntary limitations on marketing of their products perhaps by offering not to market it directly to consumers or, in some instances, some companies have voluntarily limited the detailing of their product to certain specialty groups or advertising, perhaps, to only certain specialty journals.

But let me turn now into the arena where FDA starts to have some regulatory purview. The first area is in the area of labeling. There, in a black-box warning, FDA can make quite salient certain risk information, certain contraindications or other conditions that they feel are appropriate to the safe use of a product.

One consequence of giving a product a black-box warning is that it limits the

use of what we call reminder ads, those that simply have the product's name. In practice, it makes marketing of these products directly to consumers rather difficult; it is actually mentioning that drug product.

Other options available in labeling or relabeling a product might be to change its indication to some form of second-line use or, perhaps, to actually go so far as to contraindicate its use in certain patient populations.

Another broad tier of interventions that might be taken would be in the form of some kind of targeted education or outreach. This can go to clinicians and/or to patients. This can come in the form of public announcements or "Dear Healthcare Practitioner" letters as has been done repeatedly in the past.

One form of education directed to patients are medication guides which are, in fact, forms of patient-friendly labeling informing of risks or of the methods to avoid risks directed to proteins and, in point of fact, required to be dispensed with each prescription of that product.

There are other forms of academic detailing that have been shown in some settings to be quite successful in targeting prescribers to direct their prescribing of a product to appropriate conditions felt to support its safe use.

The next broad category that I would suggest would be what we have termed, in draft guidance, reminder systems. These have ways of reinforcing or prompting people to seek appropriate use of the product. One candidate in this area might be some form of a patient

agreement or informed consent where the patient acknowledges the risks of the product and notes that they accept them.

There have been several systems in this category also put forth where the physician makes some form of attestation on paper or otherwise that some appropriate-use condition is being met. This is the case for the drug product alosetron that has been mentioned here previously. This might be attestation in the case of these products that some form of second-line use is being followed that the patient is otherwise intolerant of other therapies.

Other reminder systems may also take the form of some limitation put on the amount of the product that is supplied in any one particular prescription or, perhaps, limitations placed on whether or not refills can be obtained.

DR. FARRAR: By physician attestation, do you mean they have to write on the prescription what it is for?

DR. TRONTELL: I can give you the details of the two systems--there may now be three--where there is usually some form the physician fills out to attest that the patient meets the appropriate conditions that might be kept on file or that might, in fact, be some condition of the product being dispensed. So, in the case of alosetron, a sticker is placed on the prescription. The pharmacist is to look for that sticker to be in place before they actually dispense the product.

The last category, short of marketing suspension, is what we have termed performance-linked access systems which, really, might otherwise be termed

some form of restricted distribution of the product. In this setting, one sets forth some defined population, either of providers or patients, and sets up a process or system that restricts access to the product to those individuals.

Pharmacists may be involved if this is a product that is available through outpatient departments. These basically imply that not every physician, pharmacist or patient is able to get the product without going through certain conditions. Those conditions are required for access and, hence, the term performance-linked access.

Examples that may be known to many in this room include the drug product clozapine, sometimes abbreviated no blood, no drug. People are required to present proof of an adequate white count before obtaining the product. Thalidomide has an extensive system of registering patients, providers and pharmacists that require input from several parties to assure that the woman obtaining the product isn't pregnant at the time of dispensing.

There are some others.

In these, just to reinforce the point, which is that the product is not dispensed, not shipped or otherwise made available to the patient unless defined conditions of minimal risk have been met.

That is a very quick run-through. I will be happy to entertain further questions.

DR. WOOD: Thanks for preparing that so quickly. Anne, a number of people have asked to have a printed preparation

of that made. I wonder if we could do that as soon as we have finished.

Are there points of discussion or questions from the Committee? Yes, Arthur?

MR. LEVIN: Anne, how many drugs do we have registries for now? It is more than one, isn't it?

DR. TRONTELL: I'm sorry. You said registries?

MR. LEVIN: Right. With Accutane, didn't we get to a registry?

DR. TRONTELL: There is not one currently in place with Accutane or isotretinoin, but some of the discussions by the Drug Safety Advisory Committee had made recommendations that one be put in place. Traditionally, when you get into this last category of restricted distribution, it is very difficult to put one in place without some form of registration. You really need a list of who can and who may not, in fact, prescribe the product. So registration is almost a condition of putting up the restrictions.

MR. LEVIN: Just one other question. In the beginning, you labeled something as voluntary. How would you characterize all of these other risks? Is this a negotiated--in other words, you have voluntary limitations on marketing, but voluntary doesn't appear anywhere else, such as with labeling or anything else. But isn't all this really a negotiation? Or does the agency have the power to say, this is the way it is going to be or it comes off the market.

DR. TRONTELL: I think that is a difficult question to answer directly. The distinction of voluntary limitations were placed here because, to my knowledge, these agreements that have been put in place relative to marketing have been ones that have been offered by the drug companies opposed to FDA trying to make any restrictions upon marketing.

Generally, all of these matters of risk management or risk minimization, there is a back-and-forth process that is directed to the feasibility of actually putting some of these systems into place.

DR. WOOD: But, in fairness, if this committee makes strong recommendations that something should be done, it would be pretty tough not to follow them, I would have thought. Dr. Platt?

DR. PLATT: Anne, questions about black-box warnings and academic detailing; does the agency have a sense overall about how well black-box warnings work? I am mindful of the fact that cisapride was withdrawn from the market after several revisions of the black box failed to reduce inappropriate prescribing below something like 25 percent of all cisapride recipients.

So that is Question No. 1. Why don't you answer that and then I will ask you about academic detailing.

DR. TRONTELL: You know, evaluations of the effectiveness of any of these programs are really limited and cisapride was certainly an instance where we saw persistence of the undesired behavior despite repeated labeling.

It is difficult to say. There are some products, I was telling Dr. Wood at the break--ketorolac has a black-box warning and indications that it should be used for a very circumscribed length of time. Our examinations of prescription-use data would suggest that there is actually very high conformance in that particular instance. So I am not sure we have enough information to predict the effectiveness of these, in particular the black-box warning.

Again, looking at the black-box warning put in place for the drug product Seldane and the occurrence of torsades de pointes in its concomitant administration with other products, there were some evaluations of that labeling intervention suggesting that upwards to 90 percent or more of inappropriate co-prescribing had been eliminated but it had not eliminated entirely and that there were still unacceptable levels persisting.

So it is a mixed picture and I would like to emphasize to everyone that, perhaps, with the exception of the restricted systems, which are put in place on a relatively limited basis because they are really quite a large undertaking and do restrict access as well as minimize risks, that we have very poor information.

The systems that register individuals, by the nature of the fact that we now have a defined population of people receiving the product, we can better estimate the adverse events and other events that are reported to us. In the case of clozapine, we can actually look at how many low white counts have been observed.

DR. WOOD: But there are other examples. The Rezulin example with multiple changes in the label to invoke

different liver-function test frequencies, there is good data on the fact that that was not followed, I guess. And the cisapride example is also true. Wasn't it bromfenac that was supposed to be for ten days and most of the patients got it for longer? So there are a lot of examples that, at best, don't provide you with much reassurance that labeling changes work.

That is not to say we shouldn't do them, but, certainly, just labeling change on their own have not been extraordinarily effective.

DR. PLATT: Right. So can I ask you about what mandatory academic detailing means? Who is responsible for developing the content? Who is responsible for delivering it? Who is responsible for overseeing compliance with an effective academic-detailing regimen?

DR. TRONTELL: This is something that I put down for--to my knowledge, I don't believe we have any mandatory academic detailing positions in place but, as one example of a form of education that, in some settings has been shown effective to alter prescribing behavior. But, to my knowledge, that is not in place.

If you go back to some of the voluntary programs, some products are largely, if not solely, limited to certain specialty groups. Some of the human-growth hormones are largely confined to pediatric endocrinologists. So that has--I don't know the particulars of how those products are detailed to those prescribers.

DR. PLATT: Right. So it is not an option for us to recommend that the agency require an academic detailing program.

DR. TRONTELL: In this component, again, these slides were assembled hastily--I think the question might be, it still fits into some realm where we might define some targeted prescribing group that we thought would be appropriate to determine which patients should receive this product. So I believe it is not an easy option to identify. It really probably relates a little bit more to some of these issues which is if there is some form of limited promotion directed toward one specialty group or a specially trained group in being able to prescribe these products.

DR. WOOD: Dr. Manzi.

DR. MANZI: Actually, my questions were answered. Thanks.

DR. WOOD: Okay. Great. Dr. Day?

DR. DAY: I just wanted to mention that, in addition to the attestation option, having people sign a piece of paper, either the physician but especially the patient, that they have read and "understand," we don't know that they really understand until we give them a comprehension test.

So, this could take the form of a very brief survey. This has been tried in Accutane. To start out with, it was a voluntary survey. Under a voluntary survey, I believe that 20 percent of the patients actually filled out the survey. I don't think that the new guidelines for what is going to happen on Accutane have been released yet, but there was

some talk that that might become mandatory.

So it doesn't need to be onerous. It can be very brief. But there might be some patients who are in such pain on a given day, give them anything, they will sign it to get their relief. But if they are going to be taking these products over the long term, we really do want to be sure they understand what the consequences are going to be.

DR. WOOD: You might sign something when you were getting your wisdom teeth out that might not be applicable later; right? Dr. D'Agostino?

DR. D'AGOSTINO: Could you just reiterate what you mean by the black-box makes Direct-To-Consumer very hard. I thought it eliminated it. So could you explain what it actually does?

DR. TRONTELL: I will actually defer to Dr. Temple to give you those details.

DR. TEMPLE: The black-box makes reminder ads impossible. How big a deal that is depends on how much reminder advertising there is. I think that is not a major thing.

But the ad to be considered appropriately balanced would have to convey the contents of the black-box in all its full unpleasantness. I think that is what Anne meant. It is hard to write an ad that is appealing to people when you are telling them about all this bad news, and that would have to be right up front.

I don't know how much you pay attention to ads, but you can't just stick it over in the place where all the small print is. It would have to be part of the

main ad, whether that is a written ad or a T.V. administration.

DR. PLATT: These ads you see on television, at the end telling you may die from this.

DR. TEMPLE: Things like that. It would have to say the bad news.

DR. MORRIS: But, Bob, that is why there is no oral contraceptive ads on T.V.? That's the point. That is black-box drug.

DR. TEMPLE: I wouldn't allege for a minute that all black-boxes make it unattractive to do them. But those ads have to tell you this bad news and, if that is so unattractive, the ad doesn't appeal anymore, that is what would make it difficult.

DR. MORRIS: But, even if there is no black-box, it has to tell you the bad news.

DR. TEMPLE: The contents of a black-box are scary and unpleasant and that is all Anne meant, that it might be hard to get an appealing ad.

DR. MORRIS: I don't want to get off the impression that, if there is a black-box, we don't have to worry about DTC.

DR. TEMPLE: No; I wouldn't say that.

DR. WOOD: No; that is exactly right. There are certainly ways to do DTC in print ads, particularly, that would be permissible with the black-box warning. They might not be pictures of young ladies skipping through pretty fields, but they would be unlikely to have just skull and crossbones on their either.

DR. TEMPLE: Right. The only thing I would allege is that we would ask that the contents of the box be featured prominently in the ad. So it still might be possible.

DR. WOOD: So one way to summarize what Anne is saying about this would be that restricting DTC should be a separate or additional issue to black-box warnings. Is that fair, Bob, even though I understand restricting DTC is not within your--

DR. TEMPLE: Right.

DR. WOOD: But it is within the rubric of the commission's recommendations.

DR. TEMPLE: It is. I think what Anne said is: We can negotiate on those things. We don't think we can ban DTC. Not everybody thinks that is true, but we don't think we can.

DR. WOOD: But we did hear yesterday that voluntary agreements can be changed pretty fast.

DR. TEMPLE: Right. Can I mention one other thing?

DR. WOOD: Sure.

DR. TEMPLE: We do have one actual rule that does allow us to impose restricted distribution under what is called Subpart H for drugs that are important and that you could only be satisfied that they were safe for use in that setting.

We have not, to my knowledge, imposed such as Subpart H restriction after approval. I could be wrong about that. I

am sure it would involve what you have been calling negotiation. But I don't think it is impossible

DR. WOOD: But that was mainly applied to oncology drugs; right? No?

DR. TEMPLE: No. Subpart H has two parts. One is approval on the basis of a surrogate. That one part. The other part is approval with limits on distribution that also make you—you would have to believe that drug couldn't be distributed safely without it. It is only supposed to refer to drugs that you really need to.

DR. WOOD: Dr. Gross?

DR. GROSS: Since direct-to-consumer advertising has been so effective for the pharmaceutical companies, have you considered doing direct-to-consumer education from the FDA's point of view, either pairing it with the ad from the pharmaceutical companies, doing it separately. I know it costs money. Maybe you could have a PDUFA extended to cover the cost for that. But I think, since it has been so effective for them, why not consider it for you?

DR. WOOD: Which one of the three of you wants to take that?

DR. TEMPLE: Actually, I am embarrassed to say I didn't hear the very beginning of the question.

DR. WOOD: The suggestion is that, in addition to direct-to-consumer advertising by drug companies, there could be direct-to-consumer advertising by the FDA to put the other ads in perspective, I guess.

DR. TEMPLE: Ah. That takes money beyond what we usually feel we have.

DR. GROSS: That is why I suggested PDUFA funding.

DR. TEMPLE: That's okay with--never mind. I am not allowed to say that.

DR. TRONTELL: What FDA does have is the opportunity, through its own broadcast resources, through MedWatch, through public-health advisories, the opportunity to speak. But, certainly, any kind of commensurate advertising campaign has largely been restricted to broad messages; you know, generics are safe, et cetera, like that.

DR. WOOD: Dr. Dworkin.

DR. DWORKIN: Are there other levels of warning in addition to black-box warnings?

DR. TRONTELL: Well, a black-box warning, or a boxed warning, is really--attaches to some of the marketing restricts that Dr. Temple described, but there is, certainly, as part of the package insert or physician labeling, a warning section that information can be placed. The black box is often set off in heavy type to make it prominent or salient to the physician, anyone looking at this product, that there is some special risk that deserves attention.

DR. WOOD: Dr. Morris? Oh; okay.

MR. LEVIN: A couple of things. One of the reasons for my no vote was this concern and that is the ability of FDA to insist on and enforce conditions which will limit the distribution and use of the drug to appropriate populations.

That said, some of the risk-management experiences we have had actually have been positive. For example, with Lotrinex, we did manage to reduce the population being prescribed the drug considerably and, I think, into the range of what experts estimated was the appropriate population.

My problem here is the time it takes to work through this. I can't remember when we had that Accutane meeting but it was over a year ago. Accutane meetings have occurred regularly over the last several decades and it just take forever, in this negotiated process, to get the things in place that are recommended and then accepted by the FDA. So I am very concerned about the time-lag issue here, that whatever we recommend today, in terms of--if we do, in terms of these kinds of options for limiting risk, that you are not going to see this in the next couple of months based on prior experience. It is going to be a long haul.

DR. WOOD: I think part of the committee's job should be to make a recommendation about how fast we should see it and light a fire under these guys. That will provide some ammunition to the FDA in their negotiations and will provide some focus to others. If they are not doing it fast enough, then we--the other option, I suppose, is to put a more restrictive position until whatever issues are resolved. Sorry. John?

DR. JENKINS: I think, as Dr. Galson said on Wednesday morning in the Introduction, we are committed to making our decision on your recommendations on these applications and these products very quickly after this

meeting. We will do everything we can to implement whatever those changes are as quickly as possible recognizing there are, sometimes, some just logistical issues that have to worked through. But we are committed to doing the action and getting it implemented as quickly as possible in this case.

DR. WOOD: There is nothing beats setting a time line, so we will probably do that. Any other comments?

DR. NISSEN: Quick question. If we think the dose is a particularly important issue, could one restrict the--could we change this label or change the doses that are marketed; for example, celecoxib is available in 100 and 200-milligram capsules. Could we limit it to the 100-milligram capsules as a way to avoid the exposure to higher doses? Is there a way to do that for the FDA?

DR. TRONTELL: That would fall in the category of what would be a reminder system; in other words, to make it difficult for people to take the higher dose. By requiring them to take more pills, they would use it up more quickly. So that would be an option that I think we would be eager to hear from the committee if that was what they thought would be the best to do.

DR. NISSEN: What I am getting is to get 800 milligrams; you would have to take 8 capsules which, obviously, would have an effect on patients not doing that.

DR. JENKINS: If I could just make a comment on that. We have to be careful that, when we make our changes, that we don't have unintended consequences of our changes. One of the things that catches people off guard sometimes is

that drug prices are not reflected, or based on the number of milligrams that are in the capsule. So 100 and a 200-milligram capsule often are very close to being the same price.

So you can have an unintended consequence for patients who need that higher dose of substantially increasing their cost by limiting the dosage that is available.

DR. WOOD: I agree with that and that is an important point, but one way, I guess, to implement that kind of change would be to have a different restriction for a different dose. You could have the 200-milligram dose with different restrictions on it than the 100-milligram dose. But we will get to that point.

DR. JENKINS: Right. Stephanie?

DR. CRAWFORD: Dr. Trontell, could the options for action from a regulatory perspective include the requirement for definitive, well-designed postmarketing surveillance studies or is that not an option?

DR. TRONTELL: I think that is something that can enter into some of the regulatory options that FDA would consider, but they are not what we have classically described as an intervention to minimize risk. So that might be a way to better characterize the risk but that is something I think I will let Dr. Jenkins reply to more definitively.

DR. JENKINS: We could clearly have the companies enter into an agreement to do a postmarketing commitment study based on your recommendations. So postmarketing commitments are not only made at the time of approval, they can

also be made after approval when a new issue comes up. We probably haven't used those as much in the past as we should have in the post-approval arena, but it is certainly something we could do based on your recommendation to what studies are essential.

DR. WOOD: And your success in getting these studies completed has not been terrific; right?

DR. JENKINS: I think that is a misstatement on a lot of levels. I think the record is much better than it is portrayed often in the media. Part of the problem in the past has been record keeping as well as the agency was not as diligent in the past as we should have been in setting time lines for when the studies should be done. We are much more strict now that we set rigorous time lines for every aspect of a study including protocol submission, enrollment, completion. That information is now publicly available on our website so you can see if companies are meeting their obligations or if they are falling behind.

DR. WOOD: Okay. Well, I have got us back on time before lunch and now we have lost some of that. So, unless there are some really important questions--oh; Dr. Shafer. All right. Dr. Shafer, is this really important?

DR. SHAFER: Yes. I think so. But I just want to say that I don't support the idea of limiting the drug by placing the burden and the hassle on patients, things that require the patient--

DR. WOOD: We will get to that issue. Just questions for Dr. Trontell.

DR. SHAFER: I am coming to the very last point on the slide here. The efforts that place the burden on the patients, themselves, I think are misdirected.

DR. WOOD: All right. Thank you very much, and thanks very much for preparing that at such short notice over your lunchtime.

MS. MALONE: I just wanted to thank him for that comment.

DR. WOOD: I beg your pardon, Dr. Trontell. There is one more question.

MS. MALONE: I just wanted to thank the last speaker for that comment.

Presentation Slides

Note: Some of the slides presented may not be included below.



Options for Action

- Voluntary limitations on marketing
 - No DTC
 - Detail, ads only to selected specialists
- Labeling
 - Black box warning
 - Limits reminder ads, makes DTC very difficult
 - Change indication to 2nd line
 - Contraindicate in select pt groups

Options

- Education/Outreach
 - Public announcements, DHCP letters
 - Medication guide for patients
 - 'Academic detailing' to targeted prescribers
- Reminders
 - Patient agreement or informed consent
 - Physician attestation of appropriate use e.g. 2nd line or intolerant of other therapies
 - Limit amount supplied, or limit refills

Options

- Performance Linked Access
 - Define an appropriate prescribing physician and/or patient group and set up a process system that restricts prescribing to them, may involve pharmacists as well
 - Examples include clozapine, thalidomide
 - Drug not dispensed/shipped unless defined conditions are met

