NCCN ONCOLOGY SUMMIT:

RECOMMENDATIONS FOR REMS STAKEHOLDERS

MAY 7, 2010 – WASHINGTON, DC

Part 1

Welcome and Introductions

William T. McGivney, PhD: Good morning. Good morning everybody. All right, terrific. I'm a time nerd. I'm a self-proclaimed time nerd, but everybody got in the room on time and everything. Wow. So we'll start on time.

I'm Bill McGivney. I'm the CEO of the National Comprehensive Cancer Network, and welcome on behalf of the NCCN and our Board of Directors. We're happy you're all here to participate in another NCCN Policy Summit, this one focused on REMS, obviously. As you know, December 7, right here in this room we had a summit discussing NCCN activities and an orientation towards comparative effectiveness research in cancer. And towards the end of the year we'll be holding our third one – hopefully in this building; we're negotiating it right now – but on all the issues that are involved in use beyond FDA-approved labeling in cancer care.

But today's focus certainly is on the ongoing efforts of all of us, everybody in this room, every organization to basically improve patient safety, patient safety profiles with respect to the use of drugs and biologics and hand in hand with that, obviously, to enhance the benefit that's derived from the application of drugs and biologics out there.

So all of us are stakeholders. NCCN institutions, clearly historically again as all you have, have been focused on, devoted to, dedicated and committed to improving patient safety. Actually, every year we've had a major National Patient Safety Summit that has involved only NCCN institutions where data and best practices, benchmarking data, excuse me, and best practices are shared among the centers with the goal, obviously, to cut down on medication errors, etc., etc.

For the first time, actually, we're going to open that up this year. It will be held October 14 in the Washington, DC, area here at the Bethesda Hyatt.

So, indeed, today's focus is on REMS, but it's also limited to the use of REMS, the REMS program in cancer care, in oncology. And as you know, we'll take a look at is it different from other areas or specialties in medicine? Are we just at the extreme maybe or maybe we're not that different. You know, our clinicians have been dealing with cytotoxic agents whose aim and goal and objective is to kill cells for years and years and years as part of the mainstay of treatment plans.

Obviously, in recent years those cytotoxic agents have been joined in a very positive manner by new agents that are more cytostatic, that have reduced adverse event profiles. So we've got a lot of experience in this area; but when you're talking about mitigation of risk in serious and life-threatening illness where the aim is actually to kill cells, this is a more difficult

issue, more difficult area. And we have experts here, people much more expert than myself to discuss those issues.

We do appreciate the fact that we have colleagues from the FDA here. In the late 1980s, I was the liaison from the American Medical Association to the Food & Drug Administration, got involved in lots of issues and learned a lot. And clearly the most important thing that I learned was the dedication and commitment of people who work for the FDA to bettering public health to improving healthcare specifically.

And just one person I work very closely, some of you may have known him — he's still alive, so know him. Stuart Nightingale who was Associate Commissioner for Health Affairs during my tenure at AMA. Just a wonderful person and a great dedicated public servant.

So we're glad you're here to contribute your expertise and your experience, and that's what it's about. We're going to have presentations, and the speaker's know I'm a time nerd. So we're limiting them to 20 minutes to provide some historical perspective, some insight into what the work group discussed and recommendations; but we're going to have time for Q&A. And when we have these roundtable discussions, as I'll discuss in a minute, we want you to be involved because you're the experts. You've considered this issue very thoroughly from your perspectives, from your organizational perspectives.

A little bit about our process. NCCN basically, as you know, has live information products and a lot of other things going on, but we're a scientific clinical organization. However, more and more based on some of our information products, we're getting more and more involved in health policy, and our staff has followed this issue. This has been a major issue as raised by the pharmacy directors at our member institutions, our pharmacy group. Some are here today. You'll hear from Phil Johnson to start here.

So we established a work group of stakeholders from different constituencies if you will. Patient advocacy, clinicians, pharmacists, nursing, oncologists, pharmacy benefits management companies, the pharmaceutical industry to discuss these important issues.

And what you're going to get today is kind of a presentation of, I would call them actually draft recommendations. They're broader recommendations. As we go along, we're going to try and elicit in our discussions from you and from panel members specific examples, specific issues that we can highlight. And eventually we're going to take this document and see how we can implement it and use our ability and our expertise in a collegial way with again stakeholders, hopefully including FDA.

So I already talked about interactivity. That's going to be the key to today. It's Friday. If we're not interactive, you're probably going to be holding your own down there trying not to nod off.

But I do want to point out, secondly, that while we are at the National Press Club, there are no press here. We discussed this. We wanted a very open discussion where people felt free to make important points about this important program.

And I didn't even show the map. There's the map. There's who NCCN is. Just briefly, NCCN was established in 1995. We're a not-for-profit organization. A requirement for membership in the NCCN is, indeed, that all member institutions be not-for-profit.

We have a variety of program areas. Just briefly most people are familiar with our Guidelines, our Compendium. We work with managed care companies and National Centers of Excellence programs. We have major outcomes databases. We are involved in developing decision assist tools using our information products. We have an internal, as I already alluded to, best practices group that looks at business operational issues and tries to improve those functions in our centers. We have big international program that's developing. And, as I say, every once in a while we dip our toe into public policy.

In terms of open disclosure, I just want everyone to know that we solicited support from a variety of organizations, including managed care companies, pharma/biotech companies, other organizations. And you can see right there, those are the organizations that have provided financial support for this program.

And we appreciate the fact that these organizations, when they do provide financial support, understand very seriously the necessary autonomy of the NCCN in terms of making all decisions about content, speakers, product, format, etc. So it's important.

So, briefly, here's the agenda. It's right in front of you. As I say, we will have a brief historical perspective from the Chair of the working group, Phil Johnson. And then we will have presentations, again focused on the, as I say, more of a public policy perspective from Peyton Howell and Scott Gottlieb. And then we'll have a panel. That panel is scheduled for about 50 minutes. So if I get up there and I ask two or three questions, and you have questions, I'm going to try and have some logical flow here. But as I say, you're the experts. We want to hear from you today along with our panel members because this is where the dialogue's going to come from. As my wife always tells me, just always remember, Bill, you're the lowest common denominator in any room that you're in. So you're the experts.

No, she doesn't say that. She always gets mad when I tell those stories. But you're the experts — so don't tell her. We want to hear from you.

And as I say, in the afternoon, we will get to equally, if not more important perspectives, in terms of perspectives of the patient, perspectives of those delivering care directly in concert with decision-making processes with patients. So I think

it'll be a fast-paced interactive day. I certainly will make my best effort to make it so.

So, let's get going on the first talk here. And the first presentation is an introduction, a review, background information. And we're happy to have the founding director of Clinical Pharmacy at H. Lee Moffitt Comprehensive Cancer Center in Tampa, Florida. Probably many of you do not know that is the third largest cancer center in the United States in terms of number of patients treated every year. So you are a busy guy down there. Phil?

REMS Introduction and Background

Philip E. Johnson, MS, RPh: Well, thank you. It is indeed a high honor and a distinct privilege to chair this task force and work with so many talented people and then to bring our thoughts before an even larger group of talented people. I look forward to the discussion and where all of this leads and to the recommendations that we're making.

I think one of the first things I wanted to do is answer the question of who we are and why we're here, and Bill did a pretty good job with that, but I wanted to put it in the context of actually the fact that we are the National Comprehensive Cancer Network. So if you look at National, drug safety really is a national concern; and it's growing more and more each year.

Comprehensive, well if you look at the nature of cancer and the complexity of it, we have to have a comprehensive approach to it.

And cancer centers take a very scientific approach. We use evidence. We develop decision algorithms to help guide us through the treatment of patients, when to make changes in that therapy, to look at the efficacy and the toxicity of drugs. And so we're very process oriented. And we look at the quality of life of the patients in these decision processes too. So we have a very comprehensive approach, all of us.

Cancer itself, we have to look at the complexity of the cancer patient, the high acuity. Cancer is certainly a critical disease. Sometimes we've made it into a chronic disease, but it's really a critical disease. And in most cancer centers, at Moffitt anyway, our average patient gets 23 drugs during the course of their therapy. Very-very, very-very comprehensive. And as Bill also alluded, the therapy we use is designed to kill human cells because cancer, after all, is a human cell.

We also exacerbate or create comorbidities. It's interesting that the number one drug that we use at most cancer centers is insulin because of the impact on the endocrine system and the affect of diabetes.

So because of all of this, the reason I'm saying this is, yes, we are presenting our position on REMS as a group of cancer experts. But we believe very strongly, the whole task force believes that what we present will apply across all of healthcare because of the intense application of all issues to cancer patients.

And the final National Comprehensive Cancer Network, we are a network. Most of the presenters today will not be members of NCCN, but we reach out and collaborate with all stakeholders; and it's really exciting to me to see, as Bill listed, all of the stakeholders working together with a common goal. Because we do have the same mission. It's the safe and effective care for our patients.

We really also want the FDA to be successful in their goals, and we're here to work with them. We're here to bring our experience.

I was walking by the FDR building yesterday, and the truth was right there chiseled in stone that all of history is but a prologue for the future. So we're going to bring our experience and our expertise together. We're going to provide some constructive criticism, and we're also going to evaluate what the current practice is and make some suggestions for strategies that will help mitigate the risk associated with drug therapy. And in the process hopefully there'll be some positive impact on other aspects of healthcare as well that our speakers will get into.

But for right now my task is to provide a little bit of a background. And so I'm trying to read this little screen up here. So if I tip my head back a little bit further, some of you will understand.

So in 1938 the Federal Food Drug and Cosmetic Act was enacted. And the FDA was given regulatory control over the use of drugs in our country, the approval and use of drugs.

In 2002 the Prescription Drug User Fee Act was created, and that established RiskMAPs; and there's approximately 30 drugs associated with RiskMAPs. And the S.T.E.P.S. program for thalidomide is one example, probably the best known example to most of us.

In 2004, there were several high profile drug safety issues. There is the Vioxx issue where Vioxx was recalled because it was associated with 28,000 deaths. And there are also other risks associated with drugs that lead to questions of why the FDA allowed these drugs on the market. Whether that was a correct accusation or not is to be determined, but they certainly came under a lot of scrutiny.

In 2008 the Institute of Medicine in a publication, "The Future of Drug Safety: Promoting and Protecting the Health of the Public," recommended that the FDA have control and authority to regulate the toxicity and the risk associated with drug therapy.

And in 2007 the FDA Amendments Act, FDAAA, was signed; and that was implemented March 28, 2008, under Title IX. It created the REMS program, the Risk Evaluation and Mitigation Strategies. And it's assumed that REMS will replace RiskMAPs in the future and that current drugs in the RiskMAP program will eventually be

grandfathered into REMS. So that's a little bit of that background.

The goals specifically stated for REMS are that they should increase the FDA's drug approval rate, that they should ensure drug safety in the approval process. And so basically looking at drug safety, both in the approval process but also make sure that we monitor and manage drug safety post-approval to make sure that as more patients use those drugs, we are actually looking for and have the ability to take action to make sure that patients are safe and not harmed or at least not inappropriately harmed for using those drugs.

The components of REMS programs, there are four potential components. Not all REMS programs contain all components, but these are the four components: a medication guide, a communication plan, Elements To Assure Safe Use or ETASUs, and then an implementation system.

The authority and accountability for regulating REMS is put to the manufacturers, and they're accountable for developing the REMS program, for certifying and educating the providers, and for actually evaluating the outcomes. But they're not given the authority to hold the providers accountable, which is a problem. And that will be addressed by our speakers later on.

They also are responsible for surveilling the effectiveness of the REMS program. Did it actually do what it was supposed to do? And there's surveillance that's required at 18 months and at 3

years; and depending on the success of the program at 3 years, it might or might not be extended to a 7-year surveillance program. That's the current structure.

The FDA has enforcement over these REMS programs, and there are several processes that they can use. But probably the most powerful are the ability to levy fines and, ultimately, to withdraw the drug from the market if necessary.

So the drugs that are selected for a REMS program are based on the size and the population that will be using that drug, the seriousness of the disease or the condition, and then the expected benefit from the drug. The traditional risk-benefit evaluation process. And when you're dealing with cancer patients, as we've already mentioned, the risk of not using the drug or using it inappropriately can be catastrophic.

And then there's the potential for adverse drug reactions and the background rate of ADRs for the population that would be using that drug or that drug category. So those are considered when a determination is made if a drug should be placed into a REMS program.

The decision also looks at drugs that currently have RiskMAPs; and, again, there's the assumption that those drugs will be grandfathered into REMS programs and eventually fall under that.

Drugs that are a new molecular entity will be considered for the need of a REMS. And if you look at the pipeline of what is in research, we can see tremendous numbers of new categories of

drugs, as our research is effective. So that opens the potential for many other types of drugs where we don't know the risk, and how are we going to make sure that it is, that these drugs are safely and appropriately used and appropriately monitored?

So the future potential drugs that could fall into a REMS program frankly scares most of us who are in oncology practice in this room. You can look at all the drugs with a black box warning, and there are several of those. You can look at all drugs — I can't read that. All hazardous drugs. And so the question is what is considered a hazardous drug? You know, there are certain definitions. The EPA, for example, considers insulin as a hazardous drug for their waste management programs. But every organization and every group has a different definition of what hazardous drugs really are. And the potential number of hazardous drugs is really phenomenal.

And so then you have future drug candidates, you know, drugs with black box warnings, all hazardous drugs, drugs with abuse potential such as opioids. And we already have one opioid with a REMS. It could be more. And then drugs that — I can't read that either. Sorry, help me. Drugs that place others, I can just turn it around. Drugs that place others as risk. Thank you, Bill. Once again guiding my vision, so thank you.

So the number really, truly can be incredible. So the, for example, if you look right now at what is currently, drugs that are currently being looked at or have programs associated with them, we have 430 drugs that have a black box warning. There's

240 drugs that as a pharmacist I'm required to give a printed package insert to the patient. There's 30 drugs in RiskMAPs. There's increased activity with the MedWatch program where adverse reactions are reported. And this is good. This is very good. We're glad to see this kind of information.

And then there's some sentinel initiatives that are more regionally focused looking at specific drug issues in specific populations. And then, of course, we have the OBRA program that was implemented several years ago where all pharmacists are required to counsel patients. And many of us know that that is a good idea, but many times it's circumvented and it's not as effective as it could or should be.

So if you look at REMS in specific, there's four components to it. There's 106 drugs that fall under the category of REMS. And this is a breakdown of the components that are required. And as you can see, each one is different. And for us as pharmacists and for other practitioners, prescribers, this gets very confusing. You know, what exactly needs to be done; and so we really will talk about, through our presentations, what needs to be the most efficient and effective way, some simple process that we can more easily implement across the board.

The group, the task force universally agreed that there really should be five characteristics of a successful REMS program. And our recommendations will target these characteristics. One is it should be patient-centric and prescriber friendly because, otherwise, and we have data to show that, frankly, the drugs just

won't be used. And, of course, the risk will go away, but so will the effectiveness of that drug.

There should be minimal drug access issues, mainly to the patient. They should not, the REMS program should not be a barrier for them to getting the effective therapy they need as efficiently and promptly as they need it. It should have an enhanced service model so it's easy to use for the providers, especially it should be easy to be certified to enroll the patient into the program.

And there should be good speed and response regarding customer service, again to both the provider and to the patient who's going to be using that drug. And then the outcomes should be fed into a shared comparative effectiveness database. When we look at comparative effectiveness evaluation, quite often we look at effectiveness of the drug. And that's the mandate under healthcare reform. But it probably should also look at the toxicity of drug because that is definitely an outcome that affects the patient's quality of life and disease progression and disease treatment.

So NCCN also does monthly surveys, and these are national or international in base. And they're focused, they're brief, and to the point. Down and dirty if you will. And so last month we looked at REMS, considering the scope of this specific project.

We surveyed clinicians across the United States, and the results were basically, talked about, it was a survey done in March 2010.

And it was designed again for registrants of NCCN but to focus on what our topic was.

The demographics of the survey, primarily the respondents were physicians, but there were also a fair number of pharmacists and midlevel nurse practitioner, physician assistant prescribers, other prescribers that responded. But the demographics primarily were from the physicians.

The practice setting was primarily the office practice, followed by institutional. But we need to bear in mind also that 70% of all cancer care, 70 to 80%, depending on the survey you look at, is provided in the physician office practice. That doesn't quite match the results, but I think, and the task force agrees, that the results are so similar that statistically it doesn't make a difference.

So the point is from this slide is that we have good representation from several practice sites, most shareholders, and I think the data that we'll provide and the conclusions we come will have general consensus across all provider bases.

The goal of REMS, the first question we ask is to check out does the goal of REMS to provide quicker and easier FDA approval hold true? Do we believe as practitioners, filling out this survey, that it really will achieve that goal?

And what we find is that there's a degree of skepticism. Okay, I didn't realize this was a progressive slide. There's a degree of skepticism. More people feel that, either have a neutral stand

or feel that it will not actually bring drugs to market sooner than not.

And if you look at it by provider type, what we see is that it's fairly consistent — and I don't know if I'm proud of this or not — but pharmacists seem to be the most skeptical. And pharmacists are probably the most skeptical because we see more of the components of the whole process than other people do. The prescribers certainly have their role, but then they pass it to us; and then we pass it to the payor. So we're kind of that, you know, between a rock and a hard place, in the middle seeing both sides. So that may lead to our skepticism. We take a course in Skepticism 101 when we go through pharmacy school. It's a mandatory requirement. But, anyway, there's a degree of skepticism across all providers.

So today's agenda, as Bill laid out, is we're going to have two sessions. There's going to be presentations. And then there's going to be a workshop, and I'm really looking forward to the comments and contributions from all of you in this workshop because that's going to feed into additional papers that are going to be presented. And what we're also hoping is that we'll expand our network, and you all will get to know each other and start working together. And the more we get together, the more we collaborate, the stronger our recommendations will be so that we're all successful because we really do, again, have the same thing in mind. We want patients to have safe and effective therapy, and we truly do want the FDA to be successful. We want

them to have an effective and an efficient process so that we can all work together and achieve that common goal.

So thank you very much. Don't go away.

Dr. McGivney: You see me limping when I get up, I'm seven months— Seven weeks posthip replacement, so getting used to my new right hip.

So let me just ask two or three questions first, and then let's open it up. So you've got a lot of experience. You said 23 drugs per patient on average.

Dr. Johnson: Yes.

Dr. McGivney: Wow. I mean I had no idea. So how many patients per year are treated at the Moffitt Center, do you know? It's about—?

Dr. Johnson: Well, yesterday, we had 885 patients that were treated there in one day. We have, that would be about 180 inpatients, and the rest were outpatients.

Dr. McGivney: Uh-huh. How many, where's Ray? How many at Memorial? How many patients do you treat at Memorial Sloan-Kettering, Ray Muller?

Raymond J. Muller, MS, RPh: Yeah, hi. We have about 450 inpatients a day and probably 3,000 outpatients would be treated a day.

Dr. McGivney: So 3,000 outpatients a day. Yup. Are you number one or number two? Is M.D. Anderson more?

Dr. Muller: Yeah, we're both very good.

Dr. McGivney: You're up there. So you had your media training yesterday too. Okay. And what's your annual drug spend down there in Florida, do you know?

Dr. Johnson: We spend about $85 million.

Dr. McGivney: $85 million on drugs.

Dr. Johnson: And then if you look at the drugs we get through manufacture assistance programs and the commercial value of the investigational drugs we use, it's over, it's about $110 or $115 million.

Dr. McGivney: Okay. So from your perspective, do you think REMS is actually going to benefit? Exert an improvement on patient safety? Just a very general question but—

Dr. Johnson: In all honesty, I think REMS will and has heightened the awareness and will improve safety. My concern is at what cost because of the huge workload that it presents. And other speakers, I know in advance that the other speakers will talk, and I don't want to steal their thunder, but it's a tremendous workload; and we have limited capacity. We have limited resources. So if we spend extra time on REMS, it's deferring work from something else that's important for patient care, for the quality of patient care.

Dr. McGivney: Well, actually, and then I do hope you have questions, but I can go all day here. But, specifically, and others will talk about the logistics, I understand. But in a big operation, I know Ray's department has, the Clinical Pharmacy Group has 280 to 290 employees; and you probably have a very large group too.

I mean so what is it? I mean do you have like three people that are dedicated to making sure that the docs are certified, the pharmacists are certified, that the docs are certified for the specific drugs I mean. How is that integrated for, I guess, the eight or nine drugs that are either supportive care or treatment related in cancer care into such a big operation?

Dr. Johnson: Okay, very quickly, we have 120 FTE, 65 pharmacists; and as I alluded to earlier, cancer care is so complex that we develop protocols or decision algorithms, treatment algorithms. So a pharmacist, we have 16 cancer programs — thoracic, breast, GI, GU, and such. And so a pharmacist is part of that program. They develop, they work with a multidisciplinary team to develop the treatment protocol following NCCN and other guidelines; and we build the risk into that. So as you're going through this protocol, it's the only way we can keep all of this straight and keep it sequenced properly. So we build the risk into it, the requirements into it. If it's enrollment of the patient, we always get preauthorization; but it's part of that whole process. Whether

it's treatment looking for efficacy or it's supportive care or if it's looking at toxicity, it's all built into our protocol.

So the pharmacists, the case managers, the social workers, the nurses are all attuned and prompted through these protocols that are developed to look for certain specific things. And, again, the criteria for some of the RiskMAPs or the REMS programs are built into that as is appropriate.

Dr. McGivney: So how do you communicate to the right people? So I mean, and again, there are two ways to ask questions. You can call for a microphone or we do have question cards in your book there.

But I mean how do you make sure, as I say, that the Medication Guide is provided with the appropriate discussion of the risks associated with the drug before the patient gets the prescription and walks out the door say for an oral?

Dr. Johnson: And so the pharmacist knows what the requirements are. And before the drug is dispensed, for example, they would make sure that the education, the patients sign the consent form that they needed. We have a list of our physicians who are certified.

We have one advantage is that all the physicians are employees of the hospital, and I know talking to people where that's not the case presents another issue because I know which of our physicians are certified. But if I was a community hospital and I wouldn't necessarily have access, so then I'm going to have to

call the physician and find out is Dr. Jones certified for this, for darbepoetin or not? And that adds to their time and also my time.

So, again, I have a distinct advantage. I can just go into our medical staff profile and see are they certified, and we have a matrix set up as to what they're certified to do, what drugs they're authorized to prescribe and all of that.

Dr. McGivney: So is that all electronic, all of it?

Dr. Johnson: It's all in our computer, yes.

Dr. McGivney: So the patient's signature, is that electronic or is that just, it's transmitted to you that the patient signed the document and, therefore, it's completely on file.

Dr. Johnson: Actually, we have two ways. They can electronically sign it or they can sign a paper copy and scanned in. Depending on the area. We're in the process of converting to a total electric signature.

Dr. McGivney: So in a big center like that, is it manageable so far?

Dr. Johnson: It's very difficult. It's really added a lot of burden to our staff. And we're actually training a couple of our technicians to work with pharmacists to do some of the more technical components of this work.

Dr. McGivney: Okay. Any questions, comments? Right. So we have two right here. Right, thanks. And could you please state your name and your affiliation. Thank you.

Kevin Zacharoff, MD, FACPE, FAAP, FACIP: Sure, Kevin Zacharoff, physician from Inflexxion. With respect to the process you mentioned with the patients signing consent, so is the pharmacy taking over the job of making sure that the patient's read the Medication Guide and understands it and then the consent is signed?

Dr. Johnson: I will tell you that it's the responsibility of the physician, but about 95% of it is split between either the clinic nurse or the pharmacist working in the clinics because most of our patients, by the time they're getting the therapy, they're seen in the clinics, the orders are written, and that's where the education takes place. Then they're admitted to the hospital. So most of this work is done before they're admitted to the hospital or admitted to our infusion center. But I'd say, I don't know exactly, but it's split fairly equally between the nurse and the pharmacist in the clinics.

Dr. McGivney: I think, Nancy, next. You had a question.

Nancy Davenport-Ennis: Yes, Nancy Davenport-Ennis of the National Patient Advocate Foundation. Thank you for your remarks.

Dr. Johnson: Thank you.

Nancy Davenport-Ennis: How does the REMS process impact the patient experience of decision making and actually the initiation of therapeutic intervention from your perspective as a pharmacist?

Dr. Johnson: Yeah, it adds complexity, and, again, this is going to be addressed in detail in a later presentation, but the wording of some of the REMS programs is very harsh and focuses on the toxicity of the drug and not the efficacy and the good it can do. For example, "This drug may contribute to your death." And being required to sign this on a monthly basis.

It also, you have a limited amount of time to spend with a patient because of the limited amount of resources. So if you have a long process, a long REMS application to review with the patient, that's going to cut into either your ability, the number of patients you're going to be able to see, which I hate to say it, but cuts into the profitability of the organization. But it also, or it cuts into how you spend your time with that patient; and that's more likely what's going to happen.

So rather than talking to you about some of your personal concerns about the drug, your feelings about the drug, your quality of life, your adherence to the drug, I'm going to be talking to you about the potential harm that might be done by this drug.

And it confuses the patient because now they're focusing more on, it shifts their focus I think more to the toxicity and the harm

it could do. It's almost like looking at the direct-to-consumer advertising that's on the television. You hear a little bit about the drug and then this list of 200 items that it could do to you. And there's been studies that show that that does, in some cases, more harm than good because people will stop taking their drug after they see that list of toxicities.

I think more, and a common theme here is going to be we need to do more research on what the true impact is because what I'm giving you is my impression and my opinion. That needs to be validated through some real large population studies to see truly what the impact is on patient care and are there ways that we can more efficiently send the message but make it a balanced and objective message to facilitate the patient's decision to receive the therapy or not because with every therapy, the patient has the right to accept it or reject it. And that's very important, especially with chemotherapy. There's always an informed consent that the patient signs in the process some way, whether it's formal or informal. They consent that I know, I've been educated about this drug, and I agreed to take it. I know the risks. I know the advantages. I know the alternatives. That's part of the whole process.

Dr. McGivney: So right over there, Ray?

Ray: Phil, thank you. Just a couple of quick comments. One, I think the content, the educational content of the mandatory Med Guides are written at such an incredibly high educational level. They use words like thrombocytopenia, neutropenia, and, you know,

so on and so forth. So I think that there really needs to be a concerted effort to quote "dumb down" that content.

The next thing I think is really very important is that I have major concerns that we are asking our patients to sign a form for which the drug company logo is mandated to be on that form, and I think that's really wrong as well. And I think all of the programs that I see are really designed based upon a manual kind of system. And, you know, those of us that are in the electronic world, it is a major technological challenge to convert a color form into some sort of data that can be electronically scanned and/or retrieved. So I hope the work group has addressed that. But certainly as Phil went through a lot of the mandated things here, you know, those are things that I think we really are quite concerned about.

Dr. McGivney: And that's what I want today. We want some real practical issues. So, Niesha, last question or comment.

Speaker: Dr. Muir also has one.

Dr. McGivney: Okay, great. Yeah, we'll do these two.

Niesha Griffith, MS, RPh: Thanks, Bill. This is Niesha Griffith. I'm the Director of Pharmacy at the James Cancer Hospital, and I just wanted, to Nancy's question, I just wanted to say something else about the impact on the patient because one of our biggest concerns, and this is really based on feedback from my staff with some of these programs, is that because this

information is actually somewhat scary in the way that it's presented, it causes a lot of anxiety.

My concern moving forward as we see more of these REMS programs with cancer drugs is that patients potentially are going to choose to not get the most efficacious therapy for them because of the intimidating approach of some of these REMS programs. So that's definitely something that we need to look at as we move forward and make recommendations.

Dr. McGivney: Thank you, Niesha. Last question, a comment?

J. Cameron Muir, MD, FAAHPM: Yeah, Dr. Cameron Muir from the American Academy of Hospice and Palliative Medicine, also locally here with Capital Hospice, and I'm a clinical faculty at Hopkins.

One of the big challenges — I trained originally in oncology — and I hear quite a bit of discussion here about the chemotherapeutic REMS. And yet chronic, persistent pain is, you know, a very, very prevalent issue in cancer management. And I wanted to just make sure that as NCCN is thinking about oncology treatment for primary anticancer therapy REMS, there's a hot, hot, hot topic here in Washington with the FDA around the REMS for long-acting opioids which is unsettled at the moment how that's going to actually play out and a tremendous opportunity I think for NCCN and each of the different folks that are here to weigh in on that issue and the challenges as you talk about profitability and time. If you're not only talking about the cancer chemotherapy REMS and then the long-acting opioid REMS,

we're going to really have a challenge with quality patient care is at least a big concern for us.

Dr. McGivney: Okay, you're right. Certainly Dr. Weinstein, who's right down at the end of the row with you, is going to be addressing that.

So, I was going to ask you one more question, but I'm not. We'll save it for later. But the question was going to be is cancer different? Is it different? You know, I remember working on the treatment ID in the late 1980s. The reason we have a treatment ID regulation is because AIDS and cancer were considered serious and life-threatening illnesses where if there were no available alternative therapies, there were special considerations given to investigational drugs. So cancer and AIDS at the time, and there were other diseases, but particularly cancer and AIDS were distinguished and picked out. But we'll address it from a REMS perspective.

So thank you, Phil. Great job.

Dr. Johnson: Thank you.

Dr. McGivney: All right, so we're going to move on; and I will introduce both of the next two speakers right now. First up will be Peyton Howell who is President of Consulting Services & Health Policy for AmerisourceBergen, and she will be followed by Scott Gottlieb who's a research fellow at the American Enterprise Institute. So the way we'll do this is you'll give your

presentations. You may then take your seats, and then we'll invite the rest of the panel up. So thanks.

NCCN REMS Work Group Recommendations, Part 1

Peyton Howell, MHA: Thank you Bill and Phil for starting us off. Scott and I are going to tag team, and I really am starting with the very practical components of REMS. So I'm behind the scenes and in the nudge task associated with managing many of these programs on behalf of manufacturers. So kind of the real world reality of what you all interface with and the challenges that exist. So we're going to jump right in.

Between the two of us, our discussion points for this half of the day are really summarized here. I'm going to kick off with the standardization-related recommendations that our work group came up with as well as some of our comments related to the development of REMS and then hand it off to Scott who will get actually into some of the trend data that you were just teased with a little bit by Phil. There's some very exciting data that comes out of that, and Scott will integrate that into some of his comments as well.

So, one piece from that data, which I think is kind of an interesting quote that came from that survey that fits some of the comments we had is "Ultimately, we are looking at patient safety, but how can that be accomplished if there's not a central tracking requirement on these patients?" And, of course, this did come from a pharmacist. So, again, that skeptical nature of

what is the purpose of REMS? Are we accomplishing our goal? And somewhat for me, this quote also alluded to the fact of the confusion about REMS because they do take so many different forms and the need for better education across the larger provider community in general. So just one of many data points coming out of that data.

Standardization. Perhaps one of the biggest areas of our discussion for our work group was around the opportunity to try and identify how could this be simplified into some of the practical comments that were just made in our discussion.

So particularly related to complex REMS, so those particularly with elements to assure safe use. They're not standardized. They're not centralized. They typically have very program-specific requirements, and they really vary in the frequency of interfaces, type of certification that may or may not be necessary, whether or not a registration-type component is even necessary.

So our group clearly thought this was an issue. There's an apparent need to really optimize several aspects of REMS when you look at it through standardization.

And there's already some very basic standardization that does exist and has been promoted by the FDA. When you think about the Med Guide template being a very important example related to that.

So we were kind of driving towards what are the next opportunities to be able to support that because you can see the uptake on those templates when they're actually put forth. It does create a clear opportunity.

All of this comes together, really echoes the comments we've already had today. The inefficiencies of the current model in the process, and that's the real challenge, the cost burden associated with it. And from afar, I think it can seem like this isn't possibly a big deal. From afar, it could seem like there's really not that many products. The reality is very different than that when you talk about a practice setting. The burden that these have are actually very real, in part because they don't fit into standardized processes. So look at cancer care, and we're all trying to become more efficient in everything we do; and these create a huge wrinkle in that, particularly now that we're looking at some REMS that could touch virtually every cancer patient. So a very different type of model is really being created.

So the administrative components of REMS is an area of opportunity that we're looking for your feedback on, and we've got some specific recommendations to share related to that. Perhaps even at a standard template or kind of base template that could be shared by the FDA to create flow. Then again to an earlier point, might actually allow some of the automation then to be adopted by utilizing that. So that was one of our big areas. Some of our other comments related to standardization and

work is that there really has to be a standard process in a timeline for the FDA to review REMS strategy, and that might be why we had some of this very skeptical comments about whether or not REMS really were supporting the efficiency of the approval process, and there's certainly concern related to that.

It seemed to us that the current process for developing and improving the REMS was inherently inefficient in how it was, almost felt like a one individual versus even echoing prior REMS that are out in the community that we're already interfacing with.

The FDA really does not routinely solicit input and feedback from the broader provider community into the final REMS. Now I recognize that manufacturers, as part of the process, do get provider feedback in terms of the usability of REMS. But from our work group and just kind of sitting there, none of them had ever been even aware of that kind of interface. I think that's a very difficult thing.

So it's one of those, in theory, there's provider feedback. In reality in our work group, we saw no opportunities for provider feedback, which is, obviously, why many of you are in the room today, to be able to help us with that.

So what happens? Well what's the impact of all this? Certainly delays in access to the medications themselves and the administrative burden associated with that is a critical one. We've already heard some comments today related to suboptimal

uptake of products and whether or not the products are being utilized appropriately is a critical concern.

And then just being able to integrate the REMS procedures into the day-to-day practice of all types of cancer care — the large centers down to that community oncology is going to be critical. And I don't think we could understate the workload impact concerns. So that was a, we probably spent several hours actually talking about the workload-related concerns associated with REMS; and we felt like standardization was a key opportunity to begin to limit that. And you'll see is there an opportunity with REMS to look at maybe four or five models that could be made consistent so that there could be an opportunity for all of the REMS-related pieces to fall into one of those buckets if you will.

So, again, opportunities and I think a big part of our recommendation. So some of the recommendations we're looking for feedback on, and for discussion, I think some of these will tee up some good discussion. We thought there was a near-term opportunity to work together to develop common procedures for certification training and enrollment into REMS and really to create a best practices type mentality.

Again, the templates and being able to create templates that were available from the FDA, given how we've seen those utilized, as soon as they're made available practically. And then that might be able to address one of the earlier very important concerns we just had related to easing electronic use of this kind of

documentation because then the forms, etc. could be integrated particularly for those that are already well advanced in terms of having that part of their process.

In the medium term, what about convening a summit with all stakeholders to develop common definitions and procedures for centralization and standardization related to REMS. Some of these we understand may be more difficult. That's why we put this as a medium term for getting feedback. But this could be going to the next level. Maybe we tackle the administrative templates first but then move forward into some of the more complex issues in that medium term.

But, clearly, understanding the broader impact of REMS was recognized as a concern. There's a lot of discussion in our group, for example, about concern related to restricted distribution and restricted specialty pharmacy networks associated with some of the REMS. Many of those are actually just byproducts of how the REMS has been created to limit or require physician enrollment, patient enrollment-type mechanism versus site enrollment. When a site enrolls, then, obviously, it kind of fits in our current procedures. And I think there was a point earlier in terms of how do you know all of the practitioners in your group are certified? So this individual prescriber challenge versus how we actually practice, which is much more at a community site level, center level, is a real challenge when you look at some of the REMS, particularly related to oncology.

And then long term, what about working with the HIT companies to really develop mechanisms so this can all be streamlined. And we know that this would be difficult to integrate REMS with these EHRs. Instead, we need to find templates to be able to support that update. So it's a yin and yang, but we know it's an important one to have on the radar. So those were three kind of big areas we're looking for your feedback related to standardization.

We recognize that manufacturers face many challenges when developing their REMS programs, and we identified kind of three big ones: Communication with the FDA and other stakeholders, including all of us regarding the development of such programs. It's very challenging for a manufacturer to be able to access the real world community in a REMS situation. That's, obviously, a challenge and restricted from a regulatory perspective.

And so, therefore, it makes it difficult to assess a successful implementation, which is why we thought that need for best practices was critical so that those could be leveraged versus each of these programs feeling so different.

And then one comment that I think was actually already made is the inability to hold providers accountable to following REMS requirements. So the manufacturer has a set of programs. They cannot hold the providers accountable to that, so there's a balancing act, right? We don't want to interfere with that patient/clinician relationship. Yet at the same time, we're

being asked to insert all this information in there. And there's a challenge there.

Certainly a lot of the things in REMS could be handled by central hubs and communicated to patients, but then you're interfering with what's going on in practice. So we know that's not the answer. But somewhere in between the two is definitely a challenge. So standardizing the process seemed to be able to help with some of these components.

This one's a little bit busier. I'm glad I have my printouts. Phil, you're not alone. Cannot read that at all.

Some of the other recommendations related to this, in terms of near term, could REMS applicants include providers as part of the discussion, again, beyond that feasibility assessment? Are there more practical ways? Without slowing down the process, because we're all very sensitive to that, that it's slow enough right now. So how do we not slow down the process in terms of access to these life-saving medicines, while at the same time being able to make sure that these processes will fit into our day-to-day practice?

Another near term recommendation to that bottom left corner is that manufacturers and the FDA must communicate early in the clinical development process regarding the risk strategy. Are there mechanisms to communicate clear time tables for this? They don't exist currently in terms of that process.

Then medium term, we really gravitated towards standardizing those core survey questions. Again, I keep using the word template because for me I can practically think what that looks like. And perhaps also a manufacturer's work group could be convened to provide input and help finalize future REMS guidance so it does, obviously, entertain those types of challenges.

Basically bringing us together to have a shared voice and coordinate REMS is what those medium term ones are about. We know those aren't easy today. Today is an important first step in that. We know it would take longer to be able to pull that all together.

And we know there's a need to have an eye to some of the broader implications of REMS, in the broader community across the entire supply chain, which is why we think it's important for us all to be dialoging with this larger group.

Then in the long term, and some of these might be pie in the sky, but you have to put them out there or you can't achieve big. But could we have a public/private advisory committee that includes clinical, professional, as well as patient efficacy societies like the ones that are here today to really guide the development of REMS-related initiatives.

And then last but not least, and Scott's going to dive into this in detail, you know, assessment. You know, how is the overall effectiveness of these programs evaluated so that we don't continue things that really aren't making the correct outcomes.

So those were six of our kind of big standardization and really advice related to interfacing also with manufacturers.

Last, Medication Guides themselves; and I'm thrilled to see some of the patient advocacy comments already. Thank you Nancy Davenport-Ennis related to this because as I knew I was presenting this piece of our discussion, it was a very important part of our day, but a part that, frankly, is often overlooked. And that's the usability of this from a patient perspective. So that technical language that we currently have, is that a key concern? How do you balance the risk versus the benefit? And the language is critical. And with oncology, we have to recognize that this is very different than outside of oncology. Specific language within the ESA's Med Guide was noted as an example. So, you know, that was brought up as a key concern in terms of the type of language we're putting in front of patients; and how is that balanced in terms of the decision for them and their future treatment?

And then just the relevance even to individual treatment situations. You know, the benefits of opioids for cancer patients far outweigh the risk. So how is that risk balanced when we talk about cancer patients, which we understand is very different than some of the broader risks. So these are some challenges that are unique to oncology.

And then assessment of patient understanding of the Med Guides. Several of our work group members had very impassioned comments related to this that, frankly, I realized I hadn't even thought

about. You know, what grade level are these Med Guides out? Can anyone understand these Med Guides? It's kind of outside of our areas. And I realize that some of them hadn't, weren't even available in terms of language barriers, etc. So we do have some needs that were very, very important.

Our recommendations related to this, first the near term really related to the Medication Guide itself. Is there an opportunity to kind of tweak the templates if you will in terms of balancing that patient perspective and look at the language, the type of language that's being utilized.

In the medium term, can we begin to really pretest those guides much more aggressively or lower the grade level assessments that are currently being utilized associated with that. Again, may be impossible to do, but we have to ask the question to make sure we're doing the best that we can. We know some of these are very, very difficult to do.

And then in the long term, you know. Is there an opportunity for providers to be able to balance those messages with their clinical message, and this was the interesting part of the discussion. Again, kind of new for me to kind of hear that perspective. But what we're referring to here, is there an easy way to be able to adapt and add on information? Not change the Med Guide, but be able to pair that with a more balanced message that reflects that prescriber.

What I learned is some of the very large cancer centers are able to do that. They have the resources to have those patient education materials that can be provided in combination. That doesn't exist in the smaller practices, in the more rural communities; and that was kind of a concern that was really new to me but a very important one in terms of patient access much more broadly.

So those were our big recommendations, and now we're going to turn it over to Scott in terms of diving into the assessment.

Dr. McGivney: As most of you know, Dr. Gottlieb is former Deputy Commissioner of the Food & Drug Administration and formerly also Senior Administrator at CMS.

Scott Gottlieb, MD: Thanks a lot. I think this works. I'm going to look at my own slides.

I want to talk about some of the findings that came out over the research that we did, both in terms of the perception from the physician community, the provider community, and also talk about some of the research that we can do to better ascertain what impact the REMS are having on clinical practice.

Phil talked about doing an assessment of the REMS, and I want to pick up there. When you look back at the implementation of REMS back from 2002 in PDUFA when there was a call for the development of guidance around REMS, there was also an expectation that we would do more to try to develop research around how REMS were

working and the practical impact it was having on risk mitigation as well as on the practice environment.

I think we really haven't done as much research as we ought to be doing, as we committed to be doing as a community around the REMS. Right now if you look at what's done, it's mostly just surveys around REM programs after they get implemented. What we haven't done is gone back and systematically evaluated these REMS and tried to map between different REMS programs and where they achieve the best risk mitigation and the level of risk mitigation that they're achieving.

Certainly if a sponsor came to FDA with a survey tool saying that their drug treated cancer, I don't think that that would suffice for the agency's requirements, their data requirements. And yet that's what we're relying on when it comes to REMS in looking at both the impact that they're having in terms of risk mitigation as well as their understanding of when certain REMS strategies match up to certain kinds of risks. And there's a lot more we can do around the science of this.

I think historically FDA hasn't really thought of social sciences as hard sciences, and there hasn't been as much investment on things like risk communication, risk mitigation, which are inherently social science endeavors. I think today's FDA focuses much more on that, and you're seeing much more emphasis among the leadership in the drug center resources put behind these kinds of strategies. But it's still a work in progress, and we're still early on in all of these endeavors.

This is just some of the thoughts, some thoughts in terms of what we need to do both near term, medium term, and long term. I think that when we start to look at these things and when we start to really assess these programs, it might be that we have to define success fairly modestly. It might be the case that we're achieving only a degree of risk mitigation with these strategies. I think that there is, at least in some parties, a reluctance to look very hard and look vigorously because that might be the answer. And we might just have to settle for that, that a REMS program, no matter how rigorous, is only going to mitigate risk to a certain degree and really keep these sort of outlier actions in check. But people still will do things that are risky within certain boundaries.

And that might be acceptable. It might be worth the cost of the REMS programs or, in fact, we might find that some of the risk management strategies are so onerous and costly that the risk mitigation that we're achieving from them really isn't effective relative to the costs that we're imposing on the system.

The good news is, and this comes from some of our survey data, do I have to click multiple times to click through it? Is that how this works? Oh, too many. The good news is that there's support for this in the provider community, and this really came out of our discussions together as well. But certainly from our survey data that providers really do embrace the concept of trying to mitigate risk in how drugs are used in the practice environment

and being willing to accept certain burdens on their own clinical practices to try to achieve that.

And this is just some of the survey data. They're going to be publishing this data, so it's going to be widely available. But we don't have copies of it. I couldn't even get a copy, so I just have my slides. I think they were worried I was going to rip off one of my op eds or something, but I might very well do that.

One of the issues that we talked about was off-label drug use and REMS, and this is a particular issue in the oncology space because the REMS are oftentimes silent or, not oftentimes, they're always silent to the off-label uses of drugs, when FDA articulates the REMS strategies in labeling.

And this is for a very clear reason. If FDA talked about REMS in the context of off-label uses of drugs and put those off-label uses into the label, it would provide support for promotion on the basis of those off-label uses. So FDA historically is sort of silent to off-label uses of drugs in labeling because of concerns that if any mention of the off-label application gets into the label, it could be the basis for promotion.

And it's sort of an unfortunate situation that the agency finds itself in by virtue of the regulation and the law because it has to be kind of, pretend it's blind to things that it knows are going on and it can't really speak intelligently to those issues.

And this certainly comes out in the oncology space where there's widespread off-label uses of drugs, and yet the REMS can't speak to those. And I'm going to get to whether or not there's certain ways to address this by relying on some third parties to implement certain aspects of the REMS with respect to off-label uses. And it's not as crazy of an idea as it sounds, FDA relying on third parties to implement some of its risk mitigation strategies; and I'll sort of explain why I think it's not a crazy idea.

So why I think it's not a crazy idea. Well this just talks about some of the things that could be done, some of the impacts of REMS on off-label prescribing. And so the question came up in our work group, can a third party be charged with implementing REMS in places where FDA can't, from a regulatory standpoint, speak to the application of the drug because it is an off-label use and FDA doesn't approve of the use? Could the National Library of Medicine be responsible for some of the labeling, the distribution of certain labeling information when it addresses off-label uses? Could other not-for-profit third parties grow up to do some of this work?

And why I think it's not a crazy idea is because when you think about it, someone mentioned the FDA's authority to implement REMS and its authorities over sponsors, that authority is very ephemeral because the FDA certainly has authority over the drug companies, for the responsibilities that the drug companies have to implement REMS. But the drug companies have absolutely no

responsibility over the end user which is a physician. There's no legal authority that a drug company has over the physicians who are required to comply with these REMS other than short of shutting the doctors access to a drug off. That might be possible with a specialty pharma product where it's distributed by a single PBM; and, in fact, some drugs have been distributed through a single PBM for purposes of controlling their distribution and use. The high dose of Crestor, for example, is distributed through a single PBM for that reason.

But that's harder and harder to do in a fragmented supply chain. And so when you think about this whole architecture that we've created, it's built on sort of ephemeral authorities. FDA has legal authority over the sponsors and can require sponsors to impose the REMS and check management of the REMS, but the sponsors really have no legal authority over the physicians who are required to actually implement these things.

And so in a system where there's sort of tenuous authorities to begin with, why you couldn't rely on a third party that might not have any legal authority over the entities either doesn't seem that sort of crazy or far a field from what we're already relying on in the system which is a system of really voluntary compliance with these things, when it comes down to the end user which is the physician and the pharmacist.

So just in summary, just some sort of summary thoughts on what we've already said. Manufacturers, providers, and the FDA, other stakeholders should collaborate to standardize the REMS

processes. This was talked about earlier. We need the development of standard assessment tools, programs. They should be more scientific. We shouldn't be relying on survey tools, but we should actually do outcome studies to see what level of risk mitigation we're achieving.

And this isn't something that needs to get done in every single drug approval situation. We should really have a better understanding of what the common risks are associated with drugs, and we understand some of the common risks. The risks of teratogenicity, the risk of diversion, the risk of a baby stealing their grandmother's fentanyl pop. We understand what the risks are that we try to mitigate, but we don't necessarily understand what the best tools are for mitigating those kinds of risks. There is historical precedent, there's been practices put in place in the past. We know some things that do seem to work, but we really haven't done really rigorous evaluations of what the best way to mitigate certain risks are; and we should have that cookbook. We should have the list of common risks, and we should have the list of validated tools used to mitigate those risks and understand what the level of risk mitigation is.

And, again, this isn't something that should happen in every drug approval. That would be burdensome. We should do this once. We should validate certain tools, and we should understand how they work. And we haven't done that scientific work. And I think this is something where FDA can collaborate with NIH, with other groups to do this kind of scientific evaluation. It's not

something that's really resourced right now, frankly. Congress imposed these authorities and these requirements on the agency, and the resources for looking at these kinds of questions was sort of miniscule relative to the scientific challenge because this is going to be, I think, hard science for the agency because of standards even for evaluating these things aren't well-developed.

And, again, getting to the impact of REMS on off-label prescribing and how we address that issue, I think, which is going to be a more meaningful issue in the future. Sometimes it's the case, however, that REMS are used to attenuate off-label prescribing, so that creates a little bit of a conundrum for the agency I think when they looked to REMS to try to confine prescribing to places where they think the risk-benefit is more favorable.

Also, we talked about, in the work group, a consideration of the unintended consequences of REMS. And I think we don't fully understand this as well as we should either. This isn't something I think that's been systematically looked at, but certainly there's a shift to utilization of drugs that don't have REMS associated with them. One of the examples that often gets cited is certain drugs for the treatment of atrial fibrillation where there's some drugs that are in-hospital use only, some drugs that aren't. And there's been a shift to the drugs that aren't, even though among providers there's a sense of they're not any safer, not much different than the drugs that have REMS

associated with them. The drugs that have REMS associated with them have the unfortunate disadvantage of having been approved more recently when REMS was a concept.

So there is a shift towards drugs. We know there's a shift towards drugs that don't have these burdens associated with them. I think we need to better understand that.

And also, the impediments that the REMS programs create in terms of access to care. The people who aren't going to be able to comply with REMS, have the infrastructure to do these kinds of things are precisely the providers who oftentimes treat people who already have problems getting access to care, whether it's busy clinics or inner city environments where providers just don't have the resources, don't have the nursing staff to do the informed consent, to hand out the material, to register for these programs.

So we're creating barriers for patients, I think, who already, in many cases, face barriers to access to care. And the example I often cite is a drug called Symlin by Amylin Pharmaceuticals. And Symlin is an insulin sensitizer, so you use it in conjunction with insulin to potentiate the actions of insulin in diabetic patients. And it's a pretty good drug. I hate to sound like a commercial for Amylin. I haven't done any work for them. Oh, I'd be happy to take a consulting contract, I just haven't done any work for them.

But it potentiates weight loss, and for brittle diabetics, it's been a pretty good drug. But FDA had legitimate concerns about the drug. In the clinical trials if you used too much insulin in conjunction with Symlin, it has a very narrow therapeutic margin. You can potentiate low blood sugar, hypoglycemia. And, in fact, in the clinical trials, there were car accidents in patients who had used too much insulin in association with Symlin and became hypoglycemic while they were driving and had a car accident.

And I think the FDA deferred approval at least two times. It might have been three times of this drug and finally approved the drug with a very rigorous risk management program that puts burdens on the physicians to do proper training with the staff and with the patients around the use of Symlin. And, in fact, the drug's been used safely on the marketplace.

But one of the realities is the drug's really only prescribed by diabetologists and endocrinologists and real super specialists. But if you look at care of diabetic patients, if you look at in the inner cities and low income environments, most of those kinds of patients will never see a diabetologist. They might see a diabetologist once in their life. They get cared for by ordinary internists like me. And so you're creating an obstacle to access for patients who already face some obstacles getting access to innovative new care.

And we need to be cognizant of that. I'm not saying that there aren't tradeoffs in this that we're just going to need to accept sometimes, but I don't think that we recognize that as much as we

should. And I don't think we measure it as much as we should be as clinicians.

So this is more exciting survey data that I don't have a copy of. One of the points I want, I'm going to leave this up a little bit and not try to talk over it too much because I think the data's interesting; and I want to give you all a chance to copy it down. But I think one of the things that's interesting here is that where you have discretion around the use of a drug, generally you're not using, you're not registering for the risk management plans. So, you know, if you're a hematologist or other doctors for that matter, you've got to register for thalidomide, right? You can't practice hematology without being able to prescribe thalidomide or Revlimid for that matter.

But, you know, if you're an oncologist, do you really need to use the fentanyl film? There's probably other options if you searched around for them that might not have as rigorous programs associated with them, as many burdens associated with them. So where doctors have discretion around the use of a drug, they're generally less inclined to register for the risk management programs. And I think that that's a real concern. That's a real concern.

Some more data. One of the points I wanted to make here is that, so this is overall participation; and you see it goes up a little bit, the overall participation. And so I think that, you know, one of the points here is that the clinicians who don't have as much discretion, whether or not they have to register with the

program, the pharmacist, for example, do. But where clinicians have more discretion because they can practice oncology without being able to prescribe a certain drug. You can't practice pharmacy without having access to all the drugs. You see less compliance associated with the risk management program.

So the doctors, the statistics on the doctors were lower than the overall statistics for the whole group. Not a lot, but they were lower than the overall statistics for the whole group, largely because a doctor can practice medicine without registering for certain programs. It's a little harder for a pharmacist who's distributing a lot of drugs not to be a part of a lot of these programs in order to do their craft, their trade.

Is everyone getting the data? There's also, you know, the other thing that is obvious in all these slides, but I'll make the point, is as the administrative burden goes up for the program, there is less compliance with the program. So, you know, when you have more burdensome programs like elements for safe use, there's less doctors who are registering for those and practitioners overall.

(ASIDE)

So this is more data among physicians who are familiar with REMS about the perception. So there's no widespread perceptions and awareness about some of these programs. I'll leave this up just for a minute.

So we can see, we saw from our data, these things, you know, as I stated before, are having an impact on what doctors, what pharmacists, what clinicians are doing in their clinical practices. And that was very clear from the data. And, again, the impact seemed to increase with the burden that the REMS was imposing on the practice environment. And you saw in the data previously that when you got into the elements of safe user, which are the most burdens on the practice environment, that's where you saw the biggest drop-off.

And so this is on, this is for just physicians. And so if you look at this slide, I'm going to show the next slide which is going to be the whole group. Or actually the next slide is a pharmacist. You're again going to see a break in the numbers between the pharmacists and the physicians where the overall numbers are higher for the pharmacists in terms of their willingness to comply with these programs. I think that gets to the issue of there's just less discretion. And when you see some ability to have discretion in terms of what you're willing to do in the practice environment, you're seeing doctors less willing to use these programs.

So, there we go. This is pharmacists.

So I'm just going to back up for the four data slides, just so I can do them in unison. So this was the first slide that I showed. You know, and this shows different drugs with varying degrees of need to include in your therapeutic armamentarium, if you're an oncologist.

And this is physician participation with these drugs again, drugs that have more burdensome requirements in terms of the risk management measures being opposed on the prescription of the drug and physician's willingness to prescribe and register for these programs. And we thought this was fairly striking, so I'm going to move on to the next slide.

And these are among, again, physicians who are familiar with the REMS. Pretty striking the number of providers who were going to refer away to another provider. That's higher than the number of providers I think who refer away their Medicaid patients, but we could look at the data.

This is the last slide. This is pharmacists. And, again, I think you see the break between the physicians and the pharmacists, I think again because we felt, looking at this data, the pharmacists had less discretion because a pharmacist really is almost obligated to be part of these programs because they're servicing a larger cohort of clinicians. And even here you see some pharmacists, some pharmacies not able to participate in these programs.

So a concluding quote, and just a concluding thought, I think when you look at the, you think about the REMS and the interplay of REMS and healthcare reform, two observations I think come out of healthcare reform when it relates to the individual physician.

The first is that practice costs are going to go up under the Healthcare Reform bill and reimbursement's going to come down.

And I think that's very clear. I don't think that's a pejorative or negative statement on healthcare reform. I think we're all seeing that right now. There's going to be a lot of new mandates imposed on individual practitioners that's going to increase their overhead costs, and clearly reimbursement has come down. It probably will continue to come down over time.

The other thing that we're seeing out of healthcare reform even now is that it's leading to a lot of vertical integration in healthcare. So you're starting to see health insurance companies buy up physician practices, and you're certainly seeing hospitals try to aggressively buy up physician practices. United Healthcare is out shopping for physician practices and clinics. A lot of the big insurers are doing that right now, and you're seeing a lot of activity among hospitals buying up doctor groups and trying to vertically integrate.

And I think that's because it's going to be much more important for the payors to have control of their networks because their ability to control costs through other means is being constrained by new regulation. Their ability to increase premiums, their ability to tweak the benefit structure is going to be constrained increasingly by regulation. So the only real way to effectively control costs within your plan is to try to control your network more closely and what you pay physicians and referral patterns as well.

So you can argue that the first one clearly makes compliance with the REMS more difficult. If a doctor sees that their margins are

shrinking, it's going to be harder to spend time and money on compliance with REMS. You might be able to postulate that in an environment where the health system itself is more integrated and it's more vertical integration. It might be easier to implement some of these programs. I don't know if that's necessarily true. That's certainly been an argument that's been made by some people in the FDA and outside the FDA that part of the problem, part of the difficulty with the risk management strategies is the fragmentation of our healthcare system. And if we did have a more vertically integrated structure, it would be easier to accomplish these kinds of tasks.

I don't know if that's true. I don't think it's ever really been empirically tested. We have captive health systems like Kaiser, but I'm not sure that they do any better of a job at mitigating risks through some of these kinds of strategies than the health system at large.

So with that I'd like to close and thank you for your time. Thanks a lot.

Dr. McGivney: Thank you. If Peyton could join our Dr. Gottlieb up at the podium, and we'll make all these slides available online by close of business next Wednesday. I was wondering if there was a secret thing going on at the NCCN, but, and interesting, the, actually, we're just going to start with Dr. Gottlieb and Peyton for a few minutes; and then we'll call you guys up. Thanks.

It's an interesting process. Based on surveys, not only ours but others, over a million unique visitors come to the NCCN website every year; and within every two weeks, we think the great majority of clinicians who make decisions in the United States about cancer patients come to our website at least once. Obviously, our guidelines are the standard of care. Well accepted. There's no question about that. Payors use NCCN Guidelines, United covers the drugs and biologics in cancer care based on the NCCN Compendium. So does Aetna. So do most managed care companies.

So it's a great, not only way to do specific surveys like this because you do get a fairly representative sample of clinicians; but also I'll say it's a great vehicle to communicate all sorts of information, potentially even information about REMS.

But, so let's talk a little bit about standardization first. And, again, I'll ask the first question. Let's just start with questions from the audience. So we'll start with our Dr. Allen here with a microphone. You need a microphone? Then we'll go to Terry Langbaum from Hopkins will be next and then—

Jeff Allen, PhD: Thank you. Jeff Allen, Friends of Cancer Research. Just two points of clarification if you could, I think one from each of you. One of the recommendations was the inclusion of providers as a way to standardize some of the REMS, the templates; and the second was with regards to the use of the utilization of third parties. Is there anything that prevents this? And I guess the reason I ask, I have, of course, haven't

been really involved in the development of any of these REMS programs, but if I ever had been asked for advice, it seemed that it was highly variable by company by company to the level of information that they so choose to share. Some of them, I think, had some pretty good justification as to why they didn't want to share that data, based on confidentiality. Others sent you a truckload of confidentiality agreements to sign. But it seemed that the burden of this was really more on the companies, more so than on the FDA. And kind of the same thing with third party utilization, right? There's nothing that precludes a company from trying to employ the resources of an NCCN or an ASCO as a tool for them to either solicit input or get the information out there.

Peyton Howell: Right. I'll take the first part because you're right. There is a part of the REMS for feasibility that manufacturers have to be a part of, but that's in the dregs of the REMS process versus kind of the real world that we're all in. So that was one of the concerns that came out from our work group and the discussions specifically was are there mechanisms to be able to bridge that specifically in terms of provider input? That's why templates and standardization that are broader and not specific to a manufacturer REMS seem to us like a potential solution that we could take an incremental approach, starting with kind of the easy administrative stuff first and build from there.

Dr. Gottlieb: There's nothing that would prevent you from partnering with a third party to help implement certain aspects of these strategies. FDA clearly has requirements under legislation for certain aspects of implementation ensuring compliance, that the sponsors are complying with the components of the REMS that are included in labeling. But there would be nothing to prevent, for example, partnering with a medical professional society to try to achieve some of these risk mitigation strategies.

I will say that, you know, in my time at FDA, we spent a lot of time and so did the folks in Cedar, including some of the people in this room, talking to medical professional societies and trying to get them more actively engaged in risk communication endeavors and risk mitigation endeavors that the FDA was obligated to get involved with and often felt uncomfortable because they don't regulate the medical practice environment, nor do they want to be regulating physicians.

And it was a very difficult thing to get the medical professional sides to be willing to take on some of these responsibilities. They threw up all kinds of excuses, some legitimate around their medical/legal limitations, some that I didn't find as compelling. The only place where I found provider groups willing to participate in implementation of risk communication and risk mitigation strategies to a degree was on the medical device side of the house, groups like the Heart Rhythm Society which were very good to work with.

And I hate to sound so crass, but I always felt it was because, you know, if you take away an implantable defibrillator from electrophysiologists, they're done practicing medicine. If you take away Avandia from a diabetologist, there's a lot of other things that they can do; and it's not as much of an impact on their practice.

I think the oncology space might be different because the professional sides are so engaged in the practice of oncology. The clinicians do have a strong tie to the drugs that they're using. So I think that in the small molecule world, in the therapeutic world, that might be a place where you actually could get the professional sides more engaged in this.

Now in closing I would just say if you're looking to leverage a third party specifically to address the risk mitigation strategies as they apply to off-label uses, I think you'd have to somehow involve FDA in that because that would create I think complexities for the agency to say the least. But I think that they're all to be navigated.

Dr. McGivney: Terry?

Terry Langbaum, MAS: Terry Langbaum. I'm with the Kimmel Cancer Center at Johns Hopkins. I think that, first I'd like to say that I don't believe that those of us who are lowly hospital administrators have really been informed enough to understand just how much the implications of REMS will change hospital operations. In other words, we have to change the flow of

patients around what's happening here. I don't believe that my colleagues at Johns Hopkins, in the other 19 academic departments that also run clinical practices — and I'm in the Department of Oncology, but I have a responsibility for the Comprehensive Cancer Center, which is the service line of cancer, and we treat cancer patients in just about every department — are informed. Do the surgeons know what they'll need to do if they're going to prescribe an opioid? I don't think so. And when you look at medical oncology, and you're talking about chemotherapy drugs and opioids, I think that there hasn't been any chance to absorb exactly just how much this is going to change operations — meaning that we have to make adjustments to our IT systems or it will drive us all insane. And we have to find a way to find the time to register and train the physicians, and we have to find a way to carve out the time in our clinics which are already overburdened, where we can't take in the patients that need to be seen in a reasonable period of time today and add maybe 15 or 20 minutes or longer to any clinic visit that involves discussing chemotherapy or opioid use. And I think that we just have not even really estimated the impact of this on the day-to-day operations of taking care of cancer patients.

And I'm extremely concerned, but I would like to open up our doors to folks that are in the midst of designing the program to come and see what it's like to take care of patients. We run 100 chemotherapy chairs a day, and we have 170 patients with cancer in one building and many scattered throughout the rest of Johns Hopkins on any daily basis. And I think the day-to-day

operations are extremely important to decisions being made about the program.

Dr. McGivney: Can I just ask you Terry when you found out about REMS and how you found out?

Terry Langbaum: I found out through an NCCN Best Practices Committee discussion. We had a presentation about a year ago. So I've known this was coming, and I think folks in pharmacy have been very involved; but I don't think it's trickled down to the people that have to find the resources. We may have to add people. We certainly have to modify IT systems. And where is the money coming from? And I believe that it's everyone's responsibility that works in the healthcare world to take the waste and the cost out of healthcare, and this goes in the opposite direction of that.

Dr. McGivney: All right. And you said trickle down, but you are the Chief Administrative Officer, just so everybody knows, of the Kimmel Center at Hopkins.

Okay, yes, right here. And then we've got.

Dr. Zacharoff: Hi, just a couple of points. Peyton, I believe you mentioned in your presentation, but I didn't see it in the final recommendations, the idea about sort of a central portal. And just thinking from a clinical perspective, if I'm a clinician and I'm prescribing 6 or 7 or 10 or 12 different medications that all have REMS, it could get very confusing for me to start thinking about how I'm keeping track of it all and making sure

that everything that I've needed to do to be able to prescribe it is being done. And I can't imagine if everyone of them existed in a vacuum that I could ever do it.

With respect to disparities, I'm sure it's implied, but obviously cultural and language differences are critical pieces of the puzzle for any informed consent. And I would imagine that this could get very, very complicated in dealing with that issue. And I think it needs to be considered.

With respect to patient education, I think at the moment having somebody sign a consent is one thing; but having them be able to keep track of the likelihood of adverse events that occur in the future could make this very complicated. And then just lastly I was presented in Baltimore with a REMS for a new medication just yesterday, and the message that I got was a very mixed message in that I was told I could read the material, fill out the form, fax the form, or do nothing. And any of those possibilities would result in my being able to prescribe the medication anyway. And I think from a clinician perspective, it could sometimes be a little bit confusing. So I think all of those things need to be addressed, and I'd be interested to hear your thoughts.

Peyton Howell: Right. Excellent points. I mean I absolutely echo the patient piece, and that was a big part of our discussion. But you're right. The standardization we ended up speaking about, and knowing that to be realistic it probably had to start with some basic components, but ideally we actually did talk about a portal; and that was in our kind of pie-in-the-sky

type recommendations, realizing it may not be feasible. But certainly wanting to put that out there because, to your point, they're all different, and they're not coordinated in any way.

But at a minimum, let's take the first chunk of making some types of standardization so that we can be more efficient with this. And you're right, the educational points of, actually from both of the last comments are critical because for clinicians, this just isn't fitting together. And if there was a clear continuum of REMS that were then standardized, I think it would all start to make sense for all of us. And that was a big part of our discussion in terms of the work group.

Dr. Gottlieb: All right, there was a question in there for me.

Peyton Howell: I don't know. Does that make sense from our work group? I think I covered it. We're getting the rest of the group up here.

Roundtable Discussion, Part 1

Dr. McGivney: Yeah, I invited everybody up because, to get all the expertise up here. So we'll just continue. We have lots of questions. I would just make a comment too. I mean it's interesting because, again, NCCN does have this best practices committee that looks at business operations issues; and it's interesting in terms of, we did a little survey in terms of which institutions actually require informed consent specifically for chemotherapy. And I think the results were, now this was just a few months ago, eight of our centers actually do separate

informed consent for chemotherapeutic regimens specifically, and more had planned it. Now on top of this too you've got REMS requirements as well. So it's just interesting how this—, and I haven't even gotten into how you handle three different disease management programs — your own say at Memorial, the payors, and a specialty pharmacy disease management program. Everybody giving patients information.

So next question, we've got questions over there. Then we'll come around. Yes?

Anita Ducca: I'm Anita Ducca from the Healthcare Distribution Management Association. I have a question for Peyton on the standardization discussion. During part of your discussion you talked about recommendations for manufacturers to come together and develop common standards and definitions and procedures and things like that. And I was wondering if your group had a chance to talk about the fact that many manufacturers are competitors with each other and whether that might create any blockages to this action of coming together to develop this and how that might be addressed. That was the first part of my question.

The second part is had your group talked about anything relating to cost sharing for doing that? Whereas you might have some manufacturers who have already got REMS in place, others that might find out they need one, yet others that don't have one, but later on they do need one, and how all that would work.

Peyton Howell: Right, right.

Dr. McGivney: So before you answer, could I just, since we've got other experts up there.

Peyton Howell: Yes, please.

Dr. McGivney: So keep those questions in mind. If it were me, I would have to have written down. So Rekha Garg, what do you do? Why are you sitting up there with us?

Rekha Garg, MD, MS: So my name is Rekha Garg, and I'm with Amgen. My primary role at Amgen is within our Regulatory & Safety group. And within that group, we have actually a centralized function which is my responsibility on the development, implementation, and lifecycle management of all of REMS related to Amgen products.

And just from that perspective, as you all know from the oncology world, we do have two of the major, two of the three major products that are recently, in terms of the restricted distribution, so that's kind of my role at this point.

Dr. McGivney: Great, James Hoffman?

James M. Hoffman, PharmD, MS, BCPS: I'm the Medication Outcomes & Safety Officer at St. Jude Children's Research Hospital, and so I have a little bit of a different perspective with the pediatric focus of St. Jude. And I would say actually in pediatric oncology, we haven't been hit quite as hard with REMS yet, but I have oversight for medication safety at St. Jude.

Dr. McGivney: Great. Emily Mackler?

Emily Mackler, PharmD, BCOP: I'm a clinical pharmacist at the University of Michigan. My practice is in hematology/oncology, and I've been working with our groups there in how best to implement the REMS within our system and how to operationalize it.

Dr. McGivney: And one question I'll have for you eventually is, so you're in a matrix center, so how do you integrate REMS in cancer with other areas, other specialties. Brenda?

Brenda Sarokhan, MPH: Good morning, Brenda Sarokhan. I'm from Centocor Ortho Biotech, which is part of Johnson & Johnson. And, actually, my title is actually Senior Director of REMS because what we have done within Centocor Ortho Biotech is actually develop a very small group that sits within Medical Affairs that you could almost call a REMS Central Coordinating office if you will. But the major responsibility of our group is to ensure that all of our REMS are implemented effectively and to ensure that we submit to the FDA on time. And we work closely, we do have one of the REMS, REMS for ESAs, and we have jointly developed that with Amgen.

Speaker: It's a very effective job building, we're noticing the REMS.

Dr. McGivney: Pardon me?

Speaker: The REMS has been a very effective job—

Dr. McGivney: Well that's true. I think it is part of the Stimulus Package, actually that being an article in and of itself. Actually, I bet you have a sign on your desk that says, "REMS stops here." But, anyway, so do you want to— Or starts here maybe. Yes?

Peyton Howell?: Anita, thank you for that question. We had a very open spirit as you can tell across the group, which included manufacturers. So there was agreement in terms of standardization. We kept gravitating towards this concept of templates because that's where there was precedent. There was a template for the Med Guide, there's templates in terms of the REMS piece. So the next step would be being able to create templates related to the actual process.

So I was encouraged by that opportunity. I know early on in some of the early pre-REMS, the RiskMAPs, there are some REMS out there that were somehow really seen as proprietary. And that is, obviously, a concern because then each of these ends up looking very, very different. And you can see by the fact that we've got, actually manufacturers have had to partner together, that there could be an opportunity for that. So I left feeling very encouraged that there was an opportunity to streamline these components, acknowledging though that there are very different REMS. So it's standardization perhaps within four or five templates.

Dr. Gottlieb: I'll just pick up that point. The idea of companies developing intellectual property around REMS and

incorporating that into labeling has been looked at negatively by FDA legislators, others because it could create a barrier to approval of generics and other drugs. Celgene has intellectual property around the S.T.E.P.S. program. If someone wants to use that program which FDA acknowledges and has comfort with and recognizes that it's worked, they have to pay a small royalty to Celgene.

I don't think that a framework, a regimen like that is necessarily a bad regimen if you have certain requirements that you can't use it as an obstacle to generic entry, for example. There's things you can do, perhaps, through legislation because unless we although sponsors to develop intellectual property around these programs, sponsors aren't going to invest in the very expensive outcome studies that I talked about, trying to develop really rigorous data around these. And then it's really going to be, the burden's going to be on the government to do that kind of research; and so far the government hasn't had the resources or the wherewithal, the impetus to do that. There's been no legislation that's really provided resources for that, so it's really one or the other. Either you create an environment where there can be limited intellectual property around these programs and sponsors can earn a royalty off of them or the burden's on us. The burden's on society at large to do that kind of research if we want what I was talking about which is better outcome studies about what impact these programs are actually having.

Dr. McGivney: But don't you, I mean to say patent a REMS program or whatever, I mean that seems to go against everything you've been talking about in terms of, or the group, I won't say you personally, about standardization.

Dr. Gottlieb: Well it's one or the other. Just because there's intellectual property around a program, and there are intellectual property around some of these programs, Celgene did patent the S.T.E.P.S. program. You could still standardize around a program. People would have to pay a small royalty, presumably, or maybe not, to the sponsor that has the intellectual property. But if you want really good rigorous outcomes data on these programs, you're either going to need to provide a profit incentive to do it or, you know, you can do it with I think government resources. The government could undertake these kinds of studies.

But right now to continue to implement these programs and rely on survey data to see if they're working, I don't think really is the kind of evidence that we should settle for if we're going to continue to impose these burdens on the practice environment.

Dr. McGivney: Yup. Any other comments on this issue? We've got lots of questions and comments out there. So we'll just keep going, run with it. Dr. Throckmorton, whenever you would like, if you want to. You know, jump in and tell us we don't know what we're talking about or whatever, from the FDA. Yes?

David Campen, MD: Yeah, Dave Campen, Medical Director of Pharmacy Operations, Kaiser Permanente. For those of you that don't know, we're a vertically integrated healthcare delivery system, owned and operated PBM, 8.5 million members nationally. And to echo Terry's concerns, you know, we have integrated Epic's product in our inpatient and ambulatory systems and now their chemoinfusion product throughout 90% of our program, and we plan to complete that.

Without integration of REMS into the electronic medical record in a built-in, it creates a tremendous burden upon our caregivers and the throughput in the ability of our caregivers to comply with the standards. And you said as a long term, working with some of the technology EMR companies to develop this. That should be relooked at, and that needs to be a near term opportunity. You know, there aren't that many programs out there; and there is a great interest by these companies to make them user friendly and adapted to collect the information and be able to deliver care.

You know, many of the issues that you've discussed, we have as well, and submitted back in December a Citizen's Position to the FDA to try to address some of these concerns. We're still waiting for a response on that.

One of the issues that we have, and I'd like to hear comment on, is we try to get data back from the manufacturers that we're sending this data to. We have great difficulty, and we have pharmacy outcomes groups that work closely with our medical

groups to try to understand the impact of med safety; and I chair the Med Safety Committee, _____, California. And what strikes me as being a huge opportunity to understand aspects of med safety, if we could get access to the data we're supplying. Thank you.

Dr. McGivney: Any comments on that or, obviously, an important comment on what's self-evident. Dr. Throckmorton, did you have a comment?

Douglas Throckmorton, MD: Yeah, it is almost self-evident, but I was struck also by the lateness of the goal for electronic use. I mean as we've been talking about opiates and standing up the opiates REMS we've been investigating, the use of the electronic backbone that pharmacists use to deliver drugs day to day, the distributors use to track it. Not being a technical expert and speaking personally, that seems very robust. That is there are a lot of tools out there to find a way to make that used more systematically around all of the REMS. It seems like an obvious early thing to do, rather than something to aspire to later.

Speaker: Well and this one might be one, we all really wanted that, but we were concerned we were not being realistic; and that was a big part of our discussion, yeah.

Dr. McGivney: Can I just make a comment and see whether you agree from your experience, in your experience too.

Speaker: Um-hmm.

Dr. McGivney: So we have all sorts of information products. Very simple. Okay, 350 templates. Working with big companies to try and integrate them in a computerized physician order entry system, it's unbelievable how hard it is to do. Now, as I say, I'm a neophyte. I am the lowest common denominator in the room on this one. The issue is it is amazing to me about all the talk about electronic medical records and the lack of the ability of some very large companies in this country to take a simple set of 350 order templates and put them in electronic system. Never mind integrate that with all the different information you're getting and the requirements you need for signature. I don't know. I don't know if that's the experience in this room or not.

Speaker: That was our real world view that we had.

Dr. McGivney: Yeah.

Speaker: But we know FDA actually could help us with standardizing some of those templates on the administrative side because otherwise we do have, you know, kind of are waiting. And the more that we can be proactive on that, that was kind of the course of our discussion.

Speaker: Yeah, I think it was kind of a chicken or egg thing because it's like, if the programs are more standardized, it's much easier to make them electronic. I think that was a little bit of the thought process that if we can instill some standardization, then it's much easier to make that all electronic.

And, you know, I think what we have now is sort of this paper paradigm where each REMS that is more complex and has forms associated, makes up their own forms; and they're posted as a PDF online and you pull them down. And there's not really been much effort to think of it in an electronic way.

Speaker: And to echo that, there's differences in who is responsible for each aspect; and I really think standardizing that first is important when you think about implementing it into an electronic system.

Dr. McGivney: And I want to just follow up, and then we'll go to you and then back to the audience. But, okay, so, I mean is there coordination across specialties at University of Michigan Medical Center, not just the Cancer Center in terms of the REMS program? Or does the Cancer Center do its own REMS program or just manage it the way you want in your pharmacy? How are you doing that? You talk about, we're talking about electronic health records that would cut across systems nationally. What do you do at Michigan right now?

Dr. Mackler: You know, we coordinate efforts for each specific REMS to the people who are involved in each specific area. So we're not, we are definitely coordinating our efforts in implementing how we'll manage the ESAs amongst our inpatient group, our outpatient cancer center group, and also our outpatient dispensing pharmacies. But there's not a clear coordination amongst other REMS programs per se because, again,

the differences between them and who's involved with each of them varies.

But even that coordination has not been easy because we have differences in our systems. You know, there is a difference in our inpatient system versus our outpatient. We have differences in our formulary, inpatient and outpatient. And, again, although our physicians in the clinic practice in the hospital as well and we at least have some containment there, we have to look at it separately and include a lot of different players as we've been looking at the implementation of this program.

Dr. McGivney: Rekha?

Dr. Garg: So from our perspective, I would say that even within, from a pharma perspective, you know, having standardization forms and stuff, that's really not the issue in terms of sharing across. I mean we have a lot of things that are standardized in terms of how we do things. So that I don't think is really the challenge. I think the challenge even within our own, even from an Amgen perspective, it also relates to, it is not just, it's who the prescriber is, what the program is, and I would say today, even though we have 12 of these restricted distribution models, programs in terms of the drugs, each one is very different. And the negotiation within the FDA with the manufacturer is different.

Even my own programs that we have within Amgen are different because it all depends on what you're negotiating and what the

elements there are and what are the risks they're involved and how you're documenting them. So from our end, having electronic medical record would be excellent; but it's also the assessment piece. How do you document that? And the fact that REMS are considered labeling, that's why they're in the PDF files on the FDA website. So it's a lot of challenges that from a manufacturer that has to be taken into account, and it's not just the forms themselves that are the challenge.

Speaker: Yup, that's excellent. That was well said, especially in terms of the PDF because a lot of people aren't aware of that piece.

Dr. McGivney: We have a whole series of questions. You're making my job so easy up here it's great. Thank you.

Michael Kolodziej, MD: My name is Mike Kolodziej. I'm a medical oncologist in Albany, New York, and I'm the P&T Chairman for US Oncology.

So I'm going to put my foot right in the cow pie.

Dr. McGivney: That's why we invited you.

Dr. Kolodziej: Everyone in this room, unfortunately, and US Oncology is certainly guilty of this. I mean we're implementation beasts, right? We've got big organizations. We've got 120 FTEs and pharmacies, 60 pharmacists. Let's not forget the average oncology practice is 4 doctors. The average

pharmacy FTEs would be 0. So let me ask Scott this and then the rest of the panel can ask.

So should REMS for the community doctor be the same as REMS for the implementation beasts? It's not that the drug is more or less safe. Certainly there's a critical quantum that is required for REMS. But should there be more responsibility and maybe more rewards for the bigger beasts?

Dr. Gottlieb: I think if, I think it would be awfully hard to conceive of an environment where you bifurcated the requirements based on where the drug was being prescribed. I'm not even sure how FDA would begin to contemplate that, let alone implement it, frankly.

Dr. McGivney: Any other comment?

Speaker: Well, thank you. I just wanted to mention, I think one of the things that we've heard from Emily and from Rekha is just outlining the complexities of our organization and the complexities of fitting these programs into our organizations.

And the one thing that I think is a very important take-home point related to REMS programs is the absolute importance of stakeholder input in the development of these programs. And I really want to thank Centocor Ortho Biotech and Amgen because I think they worked very hard to get information from the field.

I presented on this topic at our Pharmacist National Oncology meeting, and I can tell you that people are not happy about this.

They're not excited about this, but it gave me a chance to make the point that I know that you all really did try. But I think from an FDA perspective, that's the one thing that I would really implore you to consider is really listening to the field, making things as easy as possible for us to incorporate into our organizations. You know, adding another form in that has to be scanned in or kept versus potentially accepting documentation that we're already doing on a risk-benefit, try to make it so it's not creating work to the extent possible yet still meeting the goals of the REMS program. I think that's just one of the most important things that we can do looking towards the future with these programs.

Dr. McGivney: You know, I'd ask the general question then, and you can respond or not. I mean are we going to reach kind of a critical threshold where we say, "Okay, we've got a lot of drugs. I'm focused on cancer. But 15 entities, maybe 5 supportive care, and 10 in treatment specifically where we're going to stop and we're going to evaluate REMS or are we going to just add all the new TKIs that come along into the REMS program before we know the effectiveness? I don't, I mean I think there probably has to be an evaluation point at some time in terms of a lot of the comments that we've had here. But does this really effectuate improvement in terms of diminishing major side effects and adverse events? I don't know if you have a comment on it.

Speaker: I just wanted to respond a little bit to the call for outside groups to be able to communicate. Just to clarify the

FDA's role here, what we do is send a letter to sponsors saying, "Here are the goals of the REMS." Now and then we start a conversation with the sponsors about how to meet those goals. You know, what pieces of paper — to use your example — what pieces of paper to send back in or whatever else it is.

I mean that's the opportunity, I think, for you all to shape how those goals are met. I mean when we need to talk about the goals, I think we need to go to advisory committees and have public comment as well. Once the goals are set on and discussed, how to implement them is another separate opportunity. And you're absolutely right. You may be collecting information that would answer the question within your usual pharmacy practice in a way that the sponsors should be aware of because it is ultimately their responsibility to come back and say, "Here's how we're going to implement those goals." So the mechanism, I guess, at least sitting where I do, would be to share a set of goals and then talk about the most efficient ways to collect that information. And that flows sort of, if you will, from the sponsors back up to the conversations that they would be having with us, at least as a first step.

Speaker: I would just add to that. I think if you look at the, and I tried to do this systematically in the *Health Affairs* article I did about three years which is arguably very dated right now because we have a lot more experience with these REMS since then. But if you look at the places where REMS have been implemented, there's a remarkable degree of homogeneity around

the kinds of things FDA was trying to achieve in the REMS. And yet there's a remarkable degree of heterogeneity in how the sponsors went about trying to achieve those things.

So, you know, stratogenicity, trying to make sure you are monitoring LFTs in a drug that has liver toxicity associated with it. The risk of anaphylaxis and an immediate kind of hypersensitivity associated with the drug. There's a handful of things where FDA has called for REMS. There's clearly outliers, there's clearly unique circumstances. But there's 10 or 12 of the same things, and yet we don't have 10 or 12 of the same exact cookie-cutter programs for trying to address those things. And I think that's what we need to get to.

And what's remarkable to me as an observer of this over time is that these REMS are not regulation of patients, per se. They're actually regulation of physicians. They're regulation of the medical practice environment by FDA. They're regulation of doctors by the federal government, and there would have been a time in history when that would have really been an anathema to the profession; and yet the profession has allowed this to happen without exerting any leadership.

The medical professional societies, the subspecialty societies in particular, I think, have had opportunity to step in to try to take on some of these tasks and play a much more active role and have not done it. And it's amazing to me to watch that.

I think if it's going to happen any place, it'll probably happen in oncology because the medical professional societies here are so much closer to the medical practice issues than in other subspecialty societies if you will.

Dr. McGivney: But when you ultimately look at it, I mean the bottom line gets to assessment. The bottom line is how are you going to assess all this. And we talked about, well, the FDA, I mean, you know, who has the money to set up the databases? Everybody's going to turn to the pharma biotech companies again and say, "Okay, it's time for another registry focused on this." And I'm not, what do you call it, backing up the medical specialty societies, but I would think when you get to the bottom line, it's a huge task. And in terms of databases to evaluate outcome on a national basis, we get a failing grade in the United States, never mind try to add on toxicity. I don't, just my perspective. All right.

David Chen, RPh, MBA: David Chen with the American Society of Health-System Pharmacists. Kind of want to dovetail on a couple of comments and maybe extenuate one of the issues of the transitions of care in that I think the FDA and the evaluation of REMS is sort of at a tipping point because we're starting to see and actually would recognize like for the opioids they step back once I think a lot of the stakeholders did comment about how it would impact the different care settings because historically so many of the REMS were in an outpatient setting you could rely on

NCPDP database. Now you're looking at hospital settings and, as you mentioned, the HER.

And so what is the interim? Is there a centralized portal? How do people access the data through these transitions of care? And I think it's inferred through standardization, but I just want to make sure it's not standardization of a form or a template. But how do we standardize things so we can carry with the patient as they go from the outpatient setting to the inpatient setting.

Dr. McGivney: Scott.

J. Scott Reid, PharmD: Scott Reid with CVS Caremark, and I'm responsible for the Specialty Pharmacy Services Group from a clinical program development standpoint.

And I just wanted to comment on some of the earlier discussion about what can be done to gain stakeholder input beyond the pharmaceutical company and the FDA, which I think is predominantly where all the discussions around what eventually finds its way into a REMS program that has to get implemented once the drug is approved occurs.

There are examples I think of best practices where certain pharmaceutical companies, you know, Ortho Biotech being one of them from my own experience, seems to be six months to a year ahead of the game, which is maybe about how long it takes I think for some REMS to be fully implemented effectively and efficiently.

But from what I have seen over the last eight years, and we probably have somewhere in the north of 25 products that we have certain REMS requirements that we manage, the problem with stakeholder input is you can't wait until the day before the FDA approves a product and makes that product available to the market possibly the following Monday to begin to consider what exactly are the implications a REMS has for a health system, a health entity, a hospital, a specialty pharmacy because more and more, I agree with Rekha, the issue isn't the standardization of forms. I mean that is, I think, if every REMS program was that, I probably wouldn't be at this meeting today.

The issue is more and more these REMS requirements do have direct impact on business process flows in a hospital, a pharmacy, what have you. It has direct implications possibly on staffing. It has direct implications on your business systems.

Large organizations cannot, who are maybe 80% electronic today and trying to get further along, cannot afford to go back to manual workarounds in the numbers of patients, in the number of prescriptions that get dispensed to implement REMS in a two-day timeframe. And if you don't, you don't have access to that drug.

I mean I can just tell you over the last five years, my organization and then we're maybe fortunate. We have resources. I can tell you, but not enough to address this issue. It's north of $5 million just for three drugs to try to implement processes and put them into our systems that will enable you if a certain response comes from a physician who has just seen a patient or in

speaking to a patient you have to stop a prescription from dispensing. It's not easy to do.

And I think there needs to be more timely engagement of the provider community, above and beyond the clinical experts. I mean the clinical experts is one piece. What do we think is going to work? But operationalizing those, that is where the challenge is; and that cannot be done efficiently and effectively after the fact. I mean the horse is already out of the barn in 90% of the REMS plans from my own perspective.

Dr. McGivney: So how does a huge organization like Caremark get in there and integrate itself in REMS programs where, again, you have to sort of basically, before you fill the prescription, I assume, basically make sure that the physician is certified to prescribe that drug, that indeed the patient has signed the informed, not consent, but the informed delivery sheet or whatever. I mean how as a huge company sitting out there in Chicago and all around the country do you do that?

Dr. Reid: The old-fashioned way, on paper, picking up telephones, calling people, writing stuff down initially if you don't have enough time.

Dr. McGivney: Yeah.

Dr. Reid: I mean if you get two days' notice on what the REMS is and you go to your IT people, you know, they can't even tell you what it's going to take to do it for another 90 days. And, oh, you want to put it in the pipeline, that's going to be another

90. So for the interim, you've got to hire people to perform these things manually. And that burden is being borne by the provider organizations. Personally, I don't think it's sustainable. You know, you can't afford in some instances, worst-case scenario, to have a 50% increase in your operating expenses per prescription. I can only imagine what it is in a hospital, in a comprehensive cancer center. You can't afford to do that very long.

Dr. McGivney: Right, right. Any comments up here on. Yes, Peyton?

Peyton Howell: Just to be clear on our recommendations, we absolutely agree with you. We're talking about standardization of process. And to James' point, the baby steps to get there. But it's all about standardization of process. It's a much bigger picture. Trying to simplify it into nuggets is, and challenge and prioritize things.

Speaker: Yeah, and I mean I think the form is sort of an end product of the process, right? I mean it's what puts in place that a physician has to be registered or a site has to be registered. So, yeah, I agree.

Speaker: And I think one thing I heard Scott say, I think it was very similar to what Terry said regarding the importance of educating stakeholders who will be involved in a REMS or who potentially could be involved in a REMS down the line. So just from a manufacturer's point of view, and actually I know there

are other industry representatives in the audience, that is a key requirement and something that we take very seriously in terms of educating the market place if you will on REMS in general and then certainly on REMS specific to that company's products.

Dr. McGivney: Okay, I have a question. I don't know, this is, and maybe it's just for the impact on cost on the federal government. Aren't associated with regulations, there are supposed to be cost impact analyses in terms of what it's going to cost the system?

Speaker: (INAUDIBLE)

Dr. McGivney: I'm sorry?

Speaker: Burden on the healthcare system.

Speaker: Have there been, I don't think there's been regulation—

Dr. McGivney: I'm just asking. I don't know.

Speaker: Yeah, so there's never been— Actually, I would say that there's never been a requirement on the FDA because when you do a regulation, you have to do a cost impact analysis. But these REMS have never been codified in regulation, just in guidance documents. Are you guys working on any regulations or just subsequent guidance documents? I mean is that an unfair question?

Speaker: (INAUDIBLE)

Speaker: All right, I don't know the answer. Okay, right. It was an innocent question actually.

Speaker: But I think that, the only thing there is in the statute is evaluating the impact of REMS on the burden of the healthcare system. How did the REMS affect the burden of the healthcare system. So you can translate that into various ways and mechanism. And even today everybody has a variety/range in terms of, within this room you know you have small community hospitals, you have large institutions. Some are using EMR. Some are not always using EMR.

So even from that perspective, it's kind of figuring out you have, the healthcare system already has a variety of different ways that they're implementing things. And then to have a REMS be something that can achieve that goal across all these different pieces of a puzzle is still a challenge from a manufacturer perspective.

And the other piece that's _____ is the assessment piece. So we you have to assess how well it's working from various mechanisms in terms of the ITs. So that's the other piece because not everybody is going to be able to do it the same way. So, again, that's another aspect that has to be taken into account.

Speaker: Yeah, you know, just stepping back, forget looking at this from a business cost standpoint, just looking at this from the impact on the patients and access standpoint. I don't think

we've done an adequate job of that, and that's difficult. That's difficult to assess that.

Dr. McGivney: Yes, questions back there.

Gary Slatko, MD, MBA: Hi, Gary Slatko, Chief Medical Officer, ParagonRx. I want to suggest maybe expanding the definition of stakeholder involvement in the program implementation. The way I think it's, the context that's being used is the impact upon stakeholders of the REMS program and the interference of the program with existing business processes and practices in medicine, pharmacy, etc.

I think that we also need to consider including stakeholders in the design of the program because I think this heterogeneity of program design that was being discussed earlier is because many of them are largely designed based on the opinions of well-meaning people sitting around a room saying, "What do you think? What should we do? What do you think?" And what's missing in that design process is the inclusion of physicians and pharmacists to better understand the process that care is being delivered, what are the desired behaviors that you want to drive at each step in the care process from original diagnosis to the decision to treat, to dispensing the product, to administering the product, to monitoring the patient. Understanding that process, analyzing it in a consistent way in every situation and then saying, "What are the desired behaviors we want? Who is the stakeholder who we want to target? And then what are reasonable interventions that could be applied to drive that behavior?

I think it's that lack of, to Scott's point earlier, this sort of scientific, process-based approach to coming up with the program in the first place that causes this vast heterogeneity. I think that's the scientific process that's missing, and I would encourage everyone to think about involving stakeholders in the actual conceptualization of the program, not just what it's impact's going to be upon them.

Speaker: Well, you know, I'll just make one observation. The REMS, this whole concept really grew up ahead of the science of how to do these kinds of things. And REMS wasn't a consequence of Vioxx. REMS was a consequence of respader drug withdrawals in the late 1990s when there was a realization that doctors weren't adhering to labeling recommendations and black box warnings. So in the case of Lotronex, doctors continued to prescribe drugs in ways that put patients at risk. In the case of Trovenge or glitazone, they weren't checking LFTs, even though the FDA had made recommendations to do that.

And there was a sense that you couldn't simply rely on black box warnings and labeling alone as a risk mitigation tool in certain cases and you needed to go one step further. And that's really where the concept of REMS grew out of. It was codified in a peculiar way in the legislation that was a consequence of Vioxx. Even though it really didn't address what the central issue was in the Vioxx sort of debacle, if you will, which was why does it take so long to figure out a drug safety question after a drug's on the market? Why can't we figure these things out sooner?

REMS really doesn't address that. It addresses the problems of the late 1990s. But in all this time, we never went back and did that scientific work if you will. We just sort of rolled into this and started to adhere to these things and impose these things without doing the fundamental scientific work that could have been done at the outset. Yet there was no, at that time there was no resources for it. There was no realization that there was really a qualified science around this. I think that realization exists now, but we haven't gone back and done the work if you will.

Dr. McGivney: Eric James.

Speaker: I wanted to make a point about one of the reasons for the heterogeneity of the programs, it is because, like you say, maybe there's different approaches that have been taken to manage different things. But I think you have to keep in mind the point that Rekha and Scott have made is that each program is designed to manage a specific risk. And so it seems logical that you're going to have different approaches to manage different risks.

So I think that goes back to the point that Scott's already made that if you can make these buckets of certain risks and then you're going to have a uniform approach to manage liver toxicity or what have you, that's a big step forward I think towards standardization. I think that's a more fundamental reason for differences across programs than just people decided different ways to implement.

Speaker: I just want to echo that slightly that I think, you know, one other thing is that this really is a great time for assessment because I think a lot of what we've seen as far as inconsistencies and changes has been because of the evolution of this process and people identifying perhaps things that may work or didn't work in the past and improving upon that or looking at how our systems are changing and how that can be implemented.

I also feel like what's been developed more recently or what we've seen in REMS more recently has become more and more complex. Just as an example, again, the most recent ESM REMS is not drug-specific. It's drug and indication-specific. And so if you look at implementation of that program in a health system and the multiple different groups in that health system and trying to implement that, it's very complex. And then you throw in the fact that non-FDA-approved indications may be exempt of all that education or what's incorporated is very challenging. So I think, you know, taking into account also that this has been under development and now is a great time for assessing what has evolved and how we can best move forward is important.

Dr. McGivney: So if you've got a REMS rug, do you look at request by a faculty member or a doc at Michigan to use it for a use beyond the FDA-approved label different from a non-REMS say oncologic therapeutic agent? You know, that's just too esoteric to even worry about given all you're doing.

Dr. Mackler: Well I think it depends on the particular REMS that has been incorporated. If you look at the thalidomide program,

for instance, that's access of the drug. And so it's really regardless of indication that is utilized. If you look at the ESA system that currently has been developed, it is dependent on indication; and we are looking at that in practice and have to.

Speaker: Yeah, I agree with that from our experience as we've had, I think that's a great way to look at it because, for example, to access Accutane for our pediatric cancer patients that use it, we have to go through the program that's designed for acne. So, you know, then we really have to deal with it. So I think that's a great way to differentiate that, the access versus the nonaccess.

Dr. McGivney: Okay, I think we're back in the audience.

Speaker: Oh, yes. I'd like to urge the task force to seriously consider mandating an educational level for these Med Guides. Again, I serve on the patient ed group, and I've read these; and actually we have software that can actually evaluate the educational level of them; and they're at 12 to 15 grade level. And, again, I think we need to realize it's all about educating our patients so that they can participate in making the right choice here. And if you will consider that the average patient that gets treated at my place gets five to ten different drugs every time they walk through the door, and we have 3,000 different patient ed things that we could give them, and then you put the next layer there that we treat patients that speak at least 18 different languages and very few, if any of these

guides, can be easily translated to Russian, Korean, Chinese, etc., this is a major challenge here.

And I think at the very least instead of saying this is really tough, etc., I would like to suggest that we put the burden of responsibility on the manufacturer and then bounce it back to the FDA that we have to recognize the fact that our patients have to be involved in their care here. And they have to be able to understand what we give them to be involved with that care.

Dr. McGivney: So what grade level do you target those 3,000 educational pieces?

Speaker: Sixth grade.

Dr. McGivney: Sixth grade, okay.

Speaker: And it's a huge challenge to do.

Dr. McGivney: Yeah, Dr. Throckmorton. Right here. Oh, you have your thing.

Dr. Throckmorton: Yeah, this is Doug from the FDA again. I'm sorry, I can't resist. It's worse than you know. I think personally, I believe it's worse than you know. The Med Guides are recognized to be less than what we'd like them to be. They are in statute, so again we are, there are challenges that need to be confronted there because some aspects of that way they're laid out is, or laid out for us. But there are other aspects of patient communication that need some attention as well, including the private groups that make the pieces of paper that you

actually get when you go to CVS and Wal-Mart and things and whether or not you're getting all of the information you need and whatever. It's another very large topic that we do hope we're going to fix and are working on pretty hard.

Speaker: Do you have legal authority over those private groups?

Dr. Throckmorton: I'm sorry?

Speaker: I mean do you have legal authority now over those, the private groups that have, including package inserts when you go to CVS?

Dr. Throckmorton: Well I'm not a lawyer nor was meant to be one, but there has been a decade's long process of looking at the effectiveness of those pieces of paper. And we've had a series of meetings recently that that effectiveness was not what it needed to be, and so we're being tasked to make some changes in that process. And that includes looking back, I think, at the Med Guides and deciding if there are better ways to go at them.

Speaker: And I think that's something actually we talked about as a group, the number of patient vehicles there are today by which a patient gets risky information. So not only is it the Med Guide, but it's also that blue piece of paper if you will, depending on where you go, that's stabled to your medication bag. So is there a better way? Is there some type of universal patient brochure that we could all work on that would effectively communicate risk to a patient as well as a benefit.

Dr. McGivney: Yeah, James?

Dr. Hoffman: Yeah, I think not all these tools either are regulated by FDA. So, again, this is an opportunity I think for the private community to develop some standards as well. That was the point I was trying to flush out. Some of these private groups that distribute information in the bag, I don't think the FDA has clear legal authority over, and that's been part of the issue in terms of standardizing them. So the community has a responsibility here and I think an opportunity.

Dr. McGivney: So, we're going to go to, I'm going to make a rhetorical comment; and then we'll go to Nancy and then we'll go to Scott. And then, oh, and Dr. Weinstein. Oh, you can make the comment first, and then I'll add on. So, Dr. Weinstein. You want to—?

Sharon Weinstein, MD, FAAHPM: Well, these are all very important points that everyone's raising. Just want to let you know this is a topic for this afternoon's agenda, so we want to hear more. Please jot down additional thoughts that you have.

Dr. McGivney: Great. So my rhetorical question just is should we change the definition of prescription drug because the legal definition of a prescription drug is that patients can't understand the risk-benefits that attend the use of that drug in patient populations enough, obviously, to prescribe for themselves. Yet we're talking about patients, and patients should be involved more and more in decision making; but I always

kind of come back to that legal definition of prescription drug that they can't understand the risk and benefits according to the law.

Anyway, that's my rhetorical question. After we get through these next two comments or questions, I just want to pose a question. It can be very brief like Bill. No, no, no, no, Bill. Is cancer different? We talked early on at the beginning about, we've dealt with cytotoxic agents for years and years. That's the goal of our therapy. Clearly other agents in psychiatry, cardiology have substantial life-threatening side effects sometimes, but is cancer different? And then the bottom line question is going to be so will this improve patient safety ultimately? So Nancy and then where are we going, Scott.

Nancy Davenport-Ennis: Thank you to the panel for stimulating points that each of you have made. I'd like to preface my observation by saying that we view all of you as seeking to find solutions to a very complicated situation. And to Bill for your observations repeatedly around cost, we concur.

But our observation is that there needs to be one fundamental study that is comprehensive as we move forward with REMS in the United States of America. There must be an evaluation of the national capacity of the information technology space in the United States today. To afford the opportunity for every hospital, every practice group, every physician office to move into the information technology highway and to evaluate the anticipated rate of attrition of the professional healthcare

workforce that will be tasked with using that information technology system in delivering the REMS to the patients in this country.

Not only is it a cost issue initially for investment into the IT space in order to have the electronic health records or the EMRs to use this, but it's also what is the impact upon the workforce that is already overburdened and understaffed in the United States of America. So we thank you for the work that you're doing on behalf of patients. We certainly know that PHRs in the pockets or on the wrist of every patient can begin to facilitate the move nationally into health information technology.

But it is so easy for us to look at REMS collection of data and say the easiest way to do it is EMR and EHR. And for those of us that serve on the national boards of information technology, we continue to be brought back to the realization today we do not have sufficient technology workforce in the country to move us singularly for the healthcare system into this space.

Dr. McGivney: I think you're right. So, Scott.

Dr. Reid: I just want to go back to the patient Medication Guide issue for a minute; and I don't want to date myself, and I haven't participated in direct patient care in probably 20 years plus now, but it always seemed to me, even back in those days, that whether they're called Medication Guides, whatever you want to call them, monographs, etc., they were just a tool to be used by a clinician in communicating and educating patients on key

issues about their medication. And I don't believe that personally that a document is an end-all in trying to achieve greater awareness of patients on how to better use their medications more safely.

So I would, you always suggest to the panel of NCCN that we need to look beyond just the guide but also look at to what other additional support needs to occur on an interactive basis with a healthcare professional or someone to make sure that not only do they read it, but they understand it and they know how to use that in terms of self-administering their medication, number one.

The second point I would just say is I think you also need to go beyond just the document and look into the area of the Internet in terms of supporting this effort. You know, in our PBM, which is somewhere north of 70 million members now, just this past year we found that 60% of the members now are going to our website for information around a number of different subjects than picking up the phone and calling today or even going to their pamphlets and their benefit guides. So at least in our organization we see around the use of medications more and more of this is being driven probably by the Internet. We're trying to develop new tools that are more interactive and enable a patient if they get to a point where they don't understand something and need support, they can immediately dial in and speak to somebody. I think that needs to be considered in the overall strategy here.

Dr. McGivney: Great, good point. All right, so the question you can answer in three sentences or less is cancer different?

Cancer care different? You know, I've already mentioned three or four times historically we manage patients with cytotoxic agents with a substantial side effect profile specifically. There are a variety, you know, both in academic settings particularly but also the community of kind of safety guides in place. I don't know, Ray at Memorial, you check the dosing, for example, what three times? Three signatures or whatever at Memorial Sloan-Kettering and probably because of all the issues that have come up over the years.

So, we'll start with you, Dr. Gottlieb. Is oncology different?

Dr. Gottlieb: Well, I don't know whether or not oncology's different from the standpoint of the drugs and their side effects. That's for the FDA to determine. I think oncology is certainly different with respect to its ability to implement risk management plans because of the complexity of the regimens that the patients are on. So if you have multiple REMS, that creates an unusual complexity.

I think oncology is different with respect to the provider community and how much you have integration between pharmacists and providers in this community relative to other therapeutic spaces. So there's more opportunity here to get it right.

Dr. McGivney: Okay, Peyton?

Peyton Howell: Yeah, I would add on that oncology is different because of the risks and benefits are different.

Dr. McGivney: Rekha?

Dr. Garg: Well, I don't think I have anything more to add onto that.

Dr. McGivney: Okay, there you go. James?

Dr. Hoffman: Yes. And this might be—

Dr. McGivney: So, yes, it is different?

Dr. Hoffman: Yes, it is different; and this might be an obvious point. But when you look at the universe of REMS, you have to keep in mind the Medication Guide is the most common type of REMS. But the complex REMS are most commonly related to oncology.

Dr. McGivney: Good point. Emily?

Dr. Mackler: Yes, I think it's different. But one thing I want to add is that I think we have to consider the, again, kind of modification of how we're treating patients and the newer availability of oral agents that— I think one benefit we've had in oncology is the contained system of giving intravenous medications and treatment. And so we really need to look at REMS as it evolves in the future and think about access to those that are perhaps not in the oncology community. And I think that is probably one important point to consider.

Dr. McGivney: Great.

Speaker: I agree with all the points made and also not only are the providers different in oncology, but I also think the patients— I mean oncology patients are very much engrained in the way that care is being delivered to them. So I say yes.

Dr. McGivney: So are you saying they're more participatory in the decision making process you think?

Speaker: Yes, yes, I believe they are.

Dr. McGivney: Okay, we're going to start with you, and with the second question I'm giving you ten seconds while I talk here. Think of your answer. So is this going to improve, is this going to decrease, if you will, the occurrence of major side effects and improve the risk-benefit proposition for patients with cancer care? The REMS program that is.

Speaker: The way the REMS are currently designed today, obviously there's a lot of room for improvement. But if it does decrease the side effects, it may be due because people are just not, providers are not using the drugs anymore. And that's not what we want.

Dr. McGivney: And we're going to talk about that this afternoon. I think that's an issue that has come up with, obviously, the clinicians who are on the panel this afternoon. Emily?

Dr. Mackler: I think there's potential.

Dr. McGivney: There's potential. Okay, very concise. I like that. Thank you. You running for office in a debate. There's

potential. That's my position and my statement. Moving on, James?

Dr. Hoffman: My opinion is I think it can be effective to especially collect like sort of the outliers, maybe the groups or physicians or pharmacists that might not catch something. It can kind of be a little bit of a safety net for those.

Dr. McGivney: So you really think, I mean this might help with the outliers, the docs that may not catch it. But the fact that they're required to actually inform patients however they implement that process will maybe hit a light bulb on both sides of the table.

Speaker: I'm looking at it as, you know, Sloan-Kettering has probably good systems to manage ESA use before the REMS even came. So, you know, but maybe some smaller place.

Dr. McGivney: Exactly.

Speaker: I think it's too early to tell at this point. We've had too many REMS, we have had 12 of these restricted REMS. I know oncology's been affected substantially because most of the REMS in the oncology are actually in the Supportive Care Oncology, not the Therapeutic Care Oncology piece of it.

And not all of them are looking at safety. They're under the, truly evaluating safety through the REMS piece of it. So I think it's really too early at this point to tell what the effect will be. There'll be a lot of consequences that have to taken into,

not just from decreased use of the drugs. So is the decreased use of the drug resulting in safety or is it physicians are not using it off-label as much because the safety issues are there? There's liability issues. So there's too many things at this point to say yes or no.

Dr. McGivney: Great. Peyton?

Peyton Howell: I love Emily's, "There's potential," answer and I'd probably just add on, "But at what cost?" Because there are the hidden costs and runs, particularly those that, for example, required restricted distribution, etc., so interrupt every part of a healthcare center. Those hidden costs are real.

Dr. McGivney: So you think it was like potentially a balloon effect here because, and Phil really raised this issue about if you're going to spend more time with patients on this one REMS issue, particularly, maybe the overall therapeutic index, as we pharmacologists call it, therapeutic index cannot be discussed as fully.

Peyton Howell: Um-hmm.

Speaker: I think clearly they've worked, and some of them have worked more than others. Clearly the opioid REMS have reduced diversion, reduced inappropriate ingestion — you know, a three-year-old getting a hold of the fentanyl pops. Clearly the REMS around Accutane have reduced the number of unprotected pregnancies that take place on that drug, although not to the level of zero that the political system demands, the unrealistic

level of the political system demands. I think the more pertinent question is what have we achieved in terms of risk mitigation and at what cost, and do the costs justify the interventions.

Dr. McGivney: Good way to end it, so we're going to break for lunch. This is the first break. Where is lunch? Can somebody yell it out?

Speaker: Same place as breakfast.

Dr. McGivney: Same place where the breakfast was, right down the hall. There should be a blue NCCN sign there. We will start promptly at 12:45. I'm keenly aware that it's Friday afternoon, but I think you'll find this afternoon's session at least as stimulating as this morning with, again, direct input by some of our clinicians, not only from NCCN but also the community.

Lunch