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LINDA BROPHY: Good afternoon, I think we will begin now. If you would take your seat, we will be ready to begin the CDER portion of the program.

I'm honored to introduce Dr. Woodcock, and she has a CDER message.

JANET WOODCOCK: Thanks, Linda. Good afternoon everyone, again. I'm very interested and I hope I will be able to hear from people and what their affiliation is and where you all come from and what your interests are during the course of the rest of this session.

Because some of you may not really know much about what we're doing or who we are in the Center for Drug Evaluation and Research, CDER, I'm going to very briefly go over some of the things that we do and what I think the current state of drug regulation is right now, what are our strengths, what are our challenges, and what questions are we seeking input on. I'm going to

talk about our level of performance, answer basic tasks that the country has asked us to do and I'm going to discuss some of the challenges that we face right now, and some of them you've heard about already during the interactive session with Dr. Henney. And finally, I'm going to talk about the questions that were asked in that session and were put up on the screen, but discuss them in the CDER context and the context of drug regulation. How are they relevant to drug regulation, and I hope we'll hear from you about that.

As far as our level of performance, I decided to use some of the charts from the Report to the Nation that we just passed out to people so you will be able to refer to that and that will provide some context about what I'm going to show you.

Basically, I think my message is that our core programs in the Center that we operate are performing

efficiently and effectively and they're serving the purposes that they were intended for. However, of course, like everything else, they could use some improvement.

If you look at New Drug Applications, this is the new medicine of different kinds that are coming on the market and changes to old medicines and dosage forms and stuff.

It does not look totally focused here. How is that; is that okay for everyone (indicating)?

You can see that the line is a number of new applications and they have gone up considerably. And the time that it's taking us to approve them -- let's start over at the 1993 on the left, and then to the right -- has dropped considerably. And this is the effect of the Prescription Drug User Fee Program, the user fee paid by industry to increase money, and the goals and timelines that were set for us. You can

study this chart, if you're interested, more thoroughly in the book.

And then if you look at whether we're meeting our goals on the New Drug Application as far as the goals that were established under the User Fee Program, which were ambitious time goals for how fast we would review applications, and most people really didn't think that the Center would be able to meet these time goals, you can see, since 1996, we have been a hundred percent on time with our New Drug Application Review. And it may be in the future we may miss one or two, but that would usually be for a very good reason.

Now, most important to the public office, are some, not all, but some of the new molecular entities. These are completely new methods that are entering the U.S. market for the first time. How are we doing on those?

What you see here is that,

since 1993, the number of new molecular entities that are approved that are going into the market have increased, although it peeked in '96 and has gone down a little bit since then, just not surprising that the '96 peek was a result of the Prescription Drug Usage Program. We have approved a great number of new molecular entities and, just as important, a review time for these new medicines is the same. It has fallen to about a year, which is our goal, and it's about the same in the overall New Drug application.

Now, equally important and previously neglected was looking at new uses of old medicines. Many of these new uses of medicines that were already on the market never came to an application before the agency. They were never really studied and they were simply adopted into medical practice. It became what you call an off-label usage. This is not necessarily good for

the medical practitioner or for the public because we need to have the drug studied for these uses and get the very best information possible on the label so people can refer to it.

And I think really good news here is that the industry is studying these uses and it's submitting them to the agency. Last year, we had 124 of these new uses for already-approved medicines submitted to the agency, and you can see that our review time is dropping for them, as well. It has dropped down to under a year and we expect an increase of improvement in new uses.

Now, equally important in a different way is our Generic Drug Program. The Generic Drug Program has economic corpse to the public because this brings competition and lowers drug prices. And the affordability of medicines is one of the issues, one of the new issues that's really emerging

now, the affordability of medicine for the public. And you can see here, again, the line is the actual number that has been submitted to us in this case, the number of generic approvals, actually.

The number of generic approvals was 344 last year, if you count all the different dosage strengths and so on. We're approving almost one generic drug everyday. So, our Generic Drug Program is doing very well. If you look at the bars which show the review times, similar to the other graphs, you can see that the review time for generic drugs has dropped remarkably over the last years in the absence of any User Fee Program and in the face of the great escalation with the number of generic drugs that are being submitted to the agency. So, we're extremely proud of our performance in this area because we haven't been supported by any additional funding.

I must say, in the context of what we talked about in the earlier session, which is the statutory review time, that the fact we need a plan to come in compliance with our statutory obligations, review time, which is the time to tell a company whether or not their generic drug application is approved or not after it's submitted, is 180 days under the statute. That is different than the time to approval because the generic drugs may go through a number of cycles before they're actually approved, but we only get about half of the generic drug applicants and answer in the 180-day timeframe. So, obviously, there are improvements that we can do there, but we think, from the point of view of the firms, and we were interested to hear what they think, that getting the overall time of getting onto the market down is more important, actually, because that gets the drug out on the market and available to provide

competition.

Now, what about once they're on the market, and I was talking about a premarket review program? Then we have marketed drugs. We regulate advertising and promotion of drugs with a very small staff of about 25 people. We try, as Dr. Henney said, to make sure that broadcast print, all other types of advertisements for drugs, the advertisements that are appearing in professional journals, the launching campaigns and so on, make sure they are balanced and not misleading and make sure that the correct information is presented there and that whether doctor, pharmacist, nurse, or patient, they don't walk away with a false impression after looking at that ad. And we think we're doing a good job there, but as you heard, there are a lot of questions, especially in the direct consumer area.

There were a lot of questions about adverse events or balance for

drugs. Once drugs are out on the market, there are going to be a lot of expected adverse events and there are going to be some new ones that are rare, or when the drug is being tried for new uses, or different populations or drug interactions.

We have built a new computer system in the last three years which we call AERS, Adverse Event Reporting System. It's a state-of-the-art system that's capable of handling this flood of reports that come in. Under the International Conference for Harmonization, which is a three-region, Japan, Europe, and the United States regulators plus industry collaboration, we've developed a harmonized terminology for the efforts to end MedDRA, which is a common name in all these regions for, say, a heart attack or whatever. You know, people have a hundred different ways to describe that. This is one step of setting up a worldwide safety network

for drugs, and it's actually functioning very well.

Our computer system uses this measure of terminology. And we hope, within the next 18 months, we will be able to have the adverse events submitted electronically to us through our electronic gateway at the agency and go directly into our computer system, and we're piloting this activity right now with some people from industry some industry sponsors. But there's much more that we need to do in adverse defense surveillance, as people brought up, and I think this is one area where the agency needs to be more active in drug regulation.

Product quality surveillance, we do a great deal with this. Product quality in lifeline is very good in the United States, much better than many other countries you may visit. In the United States, you could be very sure that what you're getting is what it says

on the bottle and that its strength is correct and that it will not crumble into dust and so forth.

And those of you who travel widely, know that isn't always the case everywhere.

For example, in test products, and we evaluate imported products, an enforcer is becoming a big issue. Just like globalization of the food supply, globalization of the drug supply, and especially involve drugs made all over the world and self industries and so forth, and it proposes a challenge for our field to figure out how to police all this.

Nevertheless, every regulated entity that makes approved drugs has to send in manufacturing supplements to the Center every time they change their processes in significant ways. And you can see that, last year, it looked like we approved 1375 of these supplements. This is a PDUFA goal because it's very

important to the industry for competitiveness to be able to modernize and to keep the plans up-to-date. So, it's important that we turn around these applications quickly and evaluate them. Our average there was five months, about five months to approve a manufacturing supplement. We're going to have more ambitious deadlines under the newly approved PDUFA agreement.

For generic drugs, I call this the gift that keeps on giving. Every time we approve a generic drug, we inherit from the field force the regulation of yet another set of manufacturing sites and processes. For generic drugs, we receive 3,000 manufacturing supplements, and we expect that to keep on growing if generic competition remains healthy in the United States, and this is a significant challenge for us.

What about drug safety? There's been a lot questions raised in

the newspapers about the safety of medicines, especially giving the record of faster review that I just talked about. People are wondering about the standards left or are we making a more cursory review. That is not the case. We have more staff and I think we're actually going to hire quality review now because science has improved. And actually, the number of patients that are evaluated in NDA is growing and the sophistication of drug evaluation is increasing.

Drug recalls are actually down, physics on drug recalls and those are in your book. And also, the rate of market withdrawal of new drugs, the actual time when a drug is approved and on the market and something terrible happens that the drug has to be taken off the market, actually, that has decreased slightly. Although I would say it's not statistically different than before, but certainly lower, and it's quite

different than in previous decades.

However, we're approving more drugs nowadays and it's quite possible that in the future, with these 30 new drugs that are coming on the market, 30 to 40 every year, that one of them, again, we will find some unacceptable rare side effect that occurs after marketing.

Linda, you're keeping me on time here; am I right? I'm almost done.

Are there key activities that the Center engages in that affect all our stakeholders that you should know about? We talked a little bit about international harmonization, but it's an extremely important activity that we're increasingly engaging in and spending more and more time every year in working with regulatory authorities around the world to try to develop common standards, to try to train regulators in underdeveloped countries. And again, our field does a lot of work in this

area.

Another challenge that people came up to me during the break and asked me about is our transition to an electronic environment. We made a commitment to go to a hamberless submission and review system by the year 2002. We have recently published, about three months ago, a guidance which allows the terms to submit totally electronic NDA, New Drug Application. This, we have no paper that we would keep, although it might have some paper copies and different things to aid the reviewers. The archive copy now can be completely electronic.

We have had, for the past couple of years, a guidance for the case report form and case report tabulations parts of the NDA, which are where the clinical data is listed. This has, so far, we think, saved about 12 million pages of paper that have been submitted to you which would have been submitted

to the agency otherwise. But this raises significant challenges for us and it's going to challenge the industry because we will start out and have voluntary submission by electronic, and eventually, we're going to have two processes side-by-side, it's too expensive. And eventually, we're going to be going to require an electronic submission, but it won't happen for a long time. People will get plenty of warning. You should be thinking about that.

Regulatory Research is very important to that part of the science base that Dr. Henney was talking about. We learn so much when we have time and some small dollars to go back into our database.

What are the implications of our regulatory position? What are the consequences of the path that we took? What did we learn about placebo controls in this area? Are they necessary?

Could we avoid them? Could we get better guidance to people who follow on afterwards, after 50 trials in rheumatoid arthritis have been done?

Only the FDA has all that data collected, and only if we have time to do the regulatory research can we help do our part to advance in the field. This is something that has really taken a hit in our constrained budget over the past few years. So, I would say we're not doing as good a job as we need to in that area, but we do our best.

Other challenges that are affecting us, the Modernization Act that you heard about that was passed by Congress made some new regulatory schemes for certain areas. One of them is pharmacy compounding, and since were in the School of Pharmacy, I think this is a relevant talk in here. There is now a new regulatory scheme for compounding of drugs, how drugs will be remade available to pharmacists, how

there will be a coalition between the State Board of Pharmacy and FDA to regulate these activities, etcetera, which drugs will be not permitted to be compounded. And we're holding a series of advisory committees and other actions. All of this is on our website and I urge those of you who are involved in pharmacy to be involved in this because we need all the input we can get. This is a very controversial area.

Positron emission tomography is a new technology that is creating diagnostic agents that are being used in patients. We were charged with developing a regulatory scheme. Health economic information was already eluded to, I think, in the previous session, a reprint of off-label uses is either other changes in the Modernization Act. We also have the radio pharmaceuticals, which we have already published a new guidance and composed ranks on, and in the reauthorization of Prescription Drug

User Fee Act, we've been very busy since that bill was passed. To do all this performance under our ever-shrinking budgetary resources, it has been a tremendous challenge for the people in the Center, and we really do need all the ideas of everyone.

The globalization of industry, I don't think many of us really recognized how fast this is happening and the profound impact it is having. And the Internet, it's been in the papers lately, selling drugs on the Internet, maybe without a prescription even.

Internet pharmacies, these are all the information age and the challenges of that age are bringing new challenges to the FDA in the way we traditionally regulated it.

Now, how am I doing as far as time?

Then the questions, what actions do you propose we take, and I'm

speaking for CDER now, from the CDER prospective, to expand our capability to incorporate science into our decision making.

We hold right now, for example, about 52, I think, scientific advisory meetings ever year, bringing in experts in different subspecialty areas. Most of these are focused, though, on specific products. Occasionally, they're focused on guidance development.

Are there ways, especially inexpensive ways, that we can better harness or incorporate the science that exists out there into our decision making? Are there ideas or suggestions that you have?

We have been having to curtail sending our scientists out for exchange programs, for sabbaticals, for learning, for training, because of budgetary constraints. And given that we can't do that right now, what other possibilities do we have?

This is similar in the exchange and integration of scientific information to better enable FDA to meet its public health responsibility throughout a product's life cycle. This is particularly germane to what happens to a drug product after it's approved. And there were a lot of questions and discussions about that, I think, in the earlier session.

Now, how do we incorporate, how do we get all that information about product use and consequences of product use into our decision-making at the agency? There may be other thoughts that you have.

This is something very dear to my heart, a concept of balancing risk against benefit in public health decision making. We feel that the people, stakeholders in this particular issue, need to really have a conversation about this because this is a systems issue and no one party is in

charge of balancing risk to benefits. It has to happen all through the chain and we need to figure out how to incorporate the understanding of the people who are assuming the risk and their judgement as well as educating them to the point that they can have a voice in the risk and benefit analysis if not all throughout everything from approval of the drug all the way to the use of the medicine. Now, this is very hard for a stakeholder to do; so, I will be interested in what you all have to say.

When we had our stakeholders meeting last year, people told us that their issue was the most important. That's very typical for a public agency, is that each stakeholder feels they have very important issues that the agency should make a top priority, but clearly, it is necessary for us to prioritize issues, and that's very difficult for us. We end up trying to put a little

bit of resources into every part of our program. And any time we try to draw back, for example, because a program is working very effectively and satisfactorily and there are other areas that we deem have greater risk, then the stakeholder for that particular area, both internal to the agency as well as external, cry foul and we're backing off on our public health responsibilities. And I think, well, what about these guys over here? You know, there are all these problems, but no, this area is fine and it should continue whatever investment of resources is invested in it. This is a very significant problem that we have.

Almost done, Linda.

The last question was, what additional actions do you propose for enhancing the communication process that allows for ongoing feedback evaluation and evolution of our modernization efforts?

Now, I feel, in particular, that CDER has made a tremendous effort in the last five years to modernize all our processes. We have tried to communicate with all our stakeholders. We have been much more successful in communicating with some groups, such industry, than others who are more diffused, such as consumers, and who have a very broad range of interests and concerns. Whatever suggestions you might have for enhancing our communications, we would appreciate, particularly if they weren't too expensive.

In summary, and I haven't gone over all our programs -- I shortened this a lot from last year -- I think it's fair to say that we're performing at a high level. We're performing very well against the tasks that we were set out, especially our traditionally defined tasks some of the newer tasks that we clearly recognize are important,

such as communicating more effectively with the outside world, we're doing them, but we certainly aren't doing them at a high level. So, I think our report card is mixed but for our core, we're performing very well. We face numerous challenges as the world changes and as our job is somewhat redefined and we invite your suggestions and comments, and that is really one of the purposes of this meeting. So, I thank you for your attention.

LINDA BROPHY: Thank you, Janet. She certainly has given us a context to have a conversation.

The next section of our discussion this afternoon, we'll hear from two of our stakeholders. We have two stakeholder presentations.

The first is Dr. King, who is a consultant from Paul G. King Consulting, and he has come to speak to us for about ten minutes.

PAUL G. KING: Well, I want to

thank everyone for letting me have the chance to say a few words. I guess I'm a contrarian in many respects.

Let me just start off by saying I'm not speaking for myself, I'm not speaking for industry and I'm not speaking for the agency. I'm speaking for the people who watch their children, parents and friends suffer from the side effects of the agency's failure to protect the public from those in the pharmaceutical industry, whose greed outweighs their concerns for the public health. That's who I'm speaking to.

As a consultant, time and time again, I have witnessed FDA-regulated companies, large and small, deliberately not comply with a law or regulation simply so they could make more money. They have done this because their management was, and is, confident that they will get away with their noncompliance -- or, if caught, profit more than their overall cost. Though my

heart goes out to the FDA in many respects, its decision not to inspect every drug establishment as often as required by law is not only wrong, it's illegal.

Beset by priorities, loss of many knowledgeable personnel under REGO, and underfunded, the agency has attempted to balance conflicting priorities instead of holding fast and protecting public health by strictly enforcing all of the current CGMP regulations for drugs.

Emboldened by an FDA that holds itself above the law and overlooks the industry's deliberate noncompliance with certain regulations, many firms, under the same cost and manpower pressures imposed on the FDA, have likewise reduced their compliance program.

Given their agency's lead, why should anyone be surprised that many of the firms it regulates currently not only ignore applicable laws and

regulations, but are also pushing for even more concessions?

For example, emboldened by their success in getting the FDA to ignore enforcement of key parts of the drug CGMP's, the industry is now pressuring the agency to allow skip lot testing, although they know full well that the CGMP regulations explicitly require the testing of each batch.

Instead of wasting time considering such initiatives, the agency again needs to begin rigorously enforcing compliance with all of the drug CGMP regulations.

This bring the public face-to-face with a major flaw in the science-based questions posed to the stakeholders.

As Dr. Henney has recognized, without knowledgable personnel who understand the true minimum requirements of both the sciences and regulations involved, the agency will continue to

accept the pseudo science that some firms submit as "valid science", and the non-compliant or violative practices that some firms are using.

Yet the reality today is that agency personnel often lack the education, training and/or experience in the regulation they are supposed to be administering or the fundamental sciences that they're supposed to understand or both required for them to properly discharge their duties.

Beyond hiring people that have the expertise it lacks and simply "providing training", what should the agency course of action be today to address these recognized deficiencies?

First, the agency needs to initially and continually establish the fundamental metric-based competency of its management, review, inspection and testing personnel in the applicable requirements of the statutes and regulations as well as the fundamentals

of all aspects of inspection science and statistics.

To do this, the agency needs to provide continual training and metric-based assessments of all such personnel to assure that said personnel, "A", understand the requirements of all applicable regulations, "B", properly assess the science submitted or applied and, "C", determine that the science submitted or applied is valid science that truly meets the minimum requirements of the current good manufacturing practices regulation.

Second, before attempting to expand its use of science, the agency needs to ensure that all firms incorporate fundamentally sound science in all areas of their submission.

Minimally, all existing and pending drug establishments' submissions need to be audited and shown to provide scientific proof that, "A", their in-process and batch-release

specifications are such that they assure, with a high level of confidence, that every article in each releasable batch will, if tested, comply with the USP's lifetime standards, but the law requires that; "('B')" All critical control points in each process step of each batch of every product need to be identified and properly controlled using valid inspection plans, most of the inspection plans that I see are just nonsense; "C", all samples tested are of appropriate size and representative of the batch from which they were taken; and "D", the number of representative samples tested is sufficient to satisfy the statistical minimums required under 21 CFR 211.165[d] For validly predicting the lifetime quality of each batch not just the present values for the samples tested.

Third, until the agency can provide the requisite in-depth ongoing metric-based training of and establish

the competency of each such employee, the agency needs to seek out, learn from, and rely upon written advice and instructions but only from those outside the agency who can prove that their advice has applied sound science in determining the true minimum requirements for compliance with a given drug CGMP as based supposedly on science.

It's amazing. I understand, as a scientist why the public in general doesn't trust scientists. It's amazing how cheaply some of us sell science to make a buck.

The preceding is but a short overview of some issues that this agency must truly address if it wishes to expand the agency's capability to incorporate state-of-the-art science or any science into its risk-based decision-making and to facilitate the exchange and integration of scientific information to better enable the FDA to

meet its public health responsibilities throughout a product's life cycle if it truly wants to protect the public.

In closing, let me thank the agency for allowing me to speak to these issues today. For those interested, my formal response to all five stakeholder questions is available on-line in the docket, and also, there are 25 copies of what I presented today more or less for anyone who would like to have a written copy. Thank you.

LINDA BROPHY: Our next speaker is Dr. Totman.

Dr. Totman comes from Consumer Healthcare Products to represent the Association.

LORNA C. TOTMAN: Thank you for giving me the opportunity to speak today. As you heard, I'm Lorna Totman, director of Scientific Affairs for the Consumer Healthcare Products Association, CHPA, which was formerly known as the Nonprescription Drug

Manufacturer's Association. The Association, founded in 1881, represents the manufacturers and distributors of national and store brand nonprescription medicines and dietary supplements. CHPA's membership comprises over 200 companies involved in the manufacture and distribution of those self-care products and their related services.

CHPA appreciates FDA's outreach to its stakeholders. Dr. Bill Soller, Senior Vice President and Director of Science and Technology, joined Commissioner Henney in the studio in Rockville, Maryland for today's video conference, and Joe Doss, our Senior Vice President and Director of Public Affairs, is speaking in the Center for Food Safety and Applied Nutrition public meeting in Chicago. We have submitted written comments in a letter to the designated docket.

My comments today on behalf of CHPA mainly addresses the first of FDA's

questions about ways the Agency can expand its capability to incorporate state-of-the-art science into its risk-based decision-making.

In answering, we would draw your attention to the switch of drugs from prescription to over-the-counter status. The public health history of Rx to OTC switch has been exemplary. Since the beginning of the OTC Review in 1972 and through the subsequent further development of the OTC NDA process of drug approval, about 80 ingredients, dosage forms, dosages and indications have been switched from Rx only to OTC. These switch products are a remarkable success story, providing significant cost savings to the public health system and important self-care therapeutics for the consumer. Examples are fluoride, vaginal antifungals, nicotine-replacement therapy, cromolyn sodium for prevention of allergy symptoms, among many others.

Importantly, under the Durham Humphrey Amendments to the FD&C Act, if a drug cannot be safely used without medical supervision, it must be labeled for sale and dispensed only by a prescription from a licensed practitioner. Otherwise, it is OTC, not restricted to Rx status.

Hence, by law and regulation in the United States, drugs are prescription by exception. In other words, if it can be OTC, it must be OTC. The law does not, however, state the approach FDA should take in determining if medical supervision is needed for a drug's safe use. In making decisions about OTC availability, FDA's Center for Drug Evaluation and Research uses a case-by-case, weight-of-the-evidence, dialogue and data-driven process. This approach is entirely consistent with the legal mandate that, if a product can be OTC, it must be OTC.

The science that provides the

foundation for Rx to OTC switch decisions has developed and improved over the years. Each novel Rx to OTC switch product has been characterized by a full array of data including, for example, studies related to post-marketing surveillance of the Rx parent, the post-marketing experience in other countries, dose-ranging studies, long-term safety studies, OTC actual use studies, label comprehension studies, and specialized safety studies in enriched populations.

FDA has demanded an ever-increasing database to support more complicated switch decisions. Hence, the proposition that a product or condition can be switched to OTC or self-care status can be regarded as a testable hypothesis. In other words, the basis for the decision is usually distilled to a basic question or questions that, if tested, would contribute meaningfully to OTC

benefit/risk decisions pertaining to OTC availability. A sponsoring company with a switch candidate, working with FDA, will define study designs to answer specific questions about the drug product's safety or effectiveness in the prospective OTC setting.

With this approach, the need for a health professional as a learned intermediary in the use of any drug for a potential or actual OTC condition is a testable hypothesis. Scientific and clinical data -- not medical opinion alone -- are the drivers for expanding the OTC paradigm with novel Rx to OTC switches.

However, in September of 1997, CDER issued a Guidance for Industry on the OTC Treatment of Hypercholesterolemia that stated: "It is CDER's view that a health care practitioner supervision in the diagnosis and ongoing management of hypercholesterolemia is essential for

safe and effective use of drug products to treat this condition and this supervision is assured within the context of prescription access to the appropriate drugs for the individual patient. CDER, therefore, believes that drugs for the treatment of hypercholesterolemia should not be sold OTC in the United States."

This decision was made after review by an FDA advisory committee of a comprehensive, well-designed, well-conducted actual use study that showed a remarkable set of study results supporting the safety and effectiveness of Questran for OTC use, as well as an equally remarkable level of interest by the American public in having widely available cholesterol-lowering agents.

CDER should adopt a policy that would require the agency to fully explain its negative switch decisions, in order to identify limitations and omissions in the sponsoring company's

submission. A sponsoring company would have the opportunity to determine what further, if any, state-of-the-art research to undertake to support a re-proposal for OTC availability of a prescription drug active ingredient. Commissioner Henney said today the agency's policies need to be grounded in science -- and that's the point I'm making. By maintaining switch as a data-driven, science-based process, FDA would be assured of having the best science to support its benefit-risk decisions about OTC availability of drug products.

In the process of developing such a CDER policy, the negative guidance on OTC cholesterol drugs would be appropriately rescinded and presumably amended. FDA should instead explain in detail the specific questions that would have to be answered by well-designed research before drugs for high cholesterol can be made available

without a prescription. This is the only way to preserve the dialogue and data-driven process that has characterized Rx to OTC switch over the last 25 years.

And now I'll shift gears a bit to comment on another important way FDA can enhance its science capability. Partnership interactions between the agency and industry give FDA's drug reviewers and compliance personnel access to evolving scientific and technical advances in the field of self-care.

CHPA has a long-standing partnership with the CDER Office of Compliance in conducting joint educational efforts, including CHPA's annual Manufacturing Controls Seminar, industry briefings, Small Business seminars, and regional meetings on specific issues identified as being manufacturing problem areas at the time. These invaluable sessions have

demonstrated an important approach to building the science base of the agency, through the collaboration of FDA with leading industry scientific and technical experts.

Our goal in these programs is to address current problem areas or evolving technology issues and create, with the agency, educational meetings that raise awareness about the identified issues, establish a higher level of understanding of the agency's expectations for current Good Manufacturing Practices, and disseminate scientific advances in the production of quality drug products. Such jointly developed educational meetings allow the agency to make use of state-of-the-art scientific expertise already available in the industry.

These efforts have an important beneficial effect on product quality. A notable example of their practical benefits was seen following the 1988

joint regional seminars on label mix-ups. The frequency of what had been the number one cause of product recalls dropped dramatically. We also understand that our educational efforts and those of other associations are regarded by the Office of Compliance as effective preventive compliance programs.

CHPA also holds an annual Research and Scientific Development Conference, with a great deal of cooperation and participation by CDER staff. This is an outstanding meeting because it enables the limits of OTC availability to be explored both conceptually and in practical exercises with hypothetical switch candidates or therapeutic categories. Our scientific conferences, and ones that may be sponsored by the Drug Information Association, The Parenteral Drugs Association or other industry groups, bring together scientists from FDA and

the regulated industries for invaluable intellectual exchanges. Participants are energized and invigorated by attending as well as having the opportunity to share new scientific information.

We ask FDA to maintain a commitment to educational partnerships with industry.

In sum, CHPA requests that FDA develop a policy within CDER to require the agency to fully explain each negative switch decision by identifying the limitations and omissions in the sponsoring company's submission, amend its guidance on OTC cholesterol drugs to omit a declaration that such drugs should not be available OTC and, instead, elaborate on the specific questions that would have to be answered before a favorable decision could be made for nonprescription status and continue the agency's commitment to educational partnerships with industry.

Thank you.

LINDA BROPHY: Thank you, Dr. Totman.

Now, we're in the section of the session where we would like to invite the FDA panelist to come up and they can take their place, their plates are in place.

While they do that, let me just warn you in response to the remaining section here for our afternoon together, we have in place four microphones located on the floor. In order for individuals to hear us all in the room as well as for the captioner on the videotape, I would really like to encourage individuals, if you have a question to please find your way to a microphone and ask your question into the microphone.

My name is Linda Brophy and I will be monitoring this section of the panel, and let me just quickly run down our list of panelists who are from FDA.

We have Dr. Nancy Smith from CDER, Dr. Janet Woodcock from CDER, we have Susan Setterberg from ORA, and Douglas Ellsworth from ORA.

So, if you would like to begin now, if you have questions, please find your way to a microphone and speak slowly and clearly and we will have our panelists here to engage in a conversation.

SANDY HARRISON: Hi, my name is Sandy Harrison. I'm a student at Temple University School of Pharmacy. My question is about direct to consumer advertising for prescription drugs. Dr. Woodcock mentioned how DeeDee Mac (ph) does a very good job considering the constraints in their resources and for most prescription drugs the promotional material would not review until the product is promotionally launched, but because of that, there can be some problems afterwards and changes may have to be made. It would seem that

that would be more costly for the companies to have to go and revise their ads. Perhaps, looking at the PDUFA program and its success with user fees for expedited review process, do you think there could be some mechanism that we could have for a user fee for promotional materials so that they could be reviewed in advance of the product launch perhaps that may even save the companies money?

JANET WOODCOCK: We will review launch materials in advance of the product launch, although there have been complaints about the timeliness of that review. And we have provided some user fee funding in that area since that is a premarketing activity. For post-market advertisement, I think there would be tremendous reluctance to have FDA prereview and I don't think there would be any enthusiasm for a User Fee Program for that. In some ways, the message gets out once the promotional material

is out there.

So, do you feel that generally, some of the direct consumer information is not balanced that's out there?

SANDY HARRISON: Yes, I think it's not balanced. I think some of it is not balanced and it's also confusing for the general lay public, which doesn't have a scientific background, that the industry or people at FDA may have. And I also think because of the power of broadcast as a print media these ads are very persuasive and it had been mentioned before about opening a dialogue with the patient and their care giver, you've already created an impression in a person's mind about the products before you even get to speak about it. That's what my concern is, that things that may be misleading will get out to the public, as it has already been done.

JANET WOODCOCK: One of the problems we've had is the brief summary

requirement. It's gibberish right now, often, that is attached to the ad. There is a requirement that a brief summary of the risk and benefits and everything be attached to the ad, and we have great difficulty creating something that would be more -- give more information, you know, in lay language. Yeah, it would be more user-friendly for consumers in directed to consumer advertising. I think that's a challenge we're going to have to meet somehow and figure out how to do that because that labelling information is fairly balanced, although I noticed it doesn't include the indication, which is very good.

But to get to your point, I mean there are two sides to this, as Jane Henney said. On one side, we know that there's vast numbers of people in this country who it's a sin of omission. They are being harmed, we know, by not being treated with safe and easily

available medicine to lower their cholesterol to prevent recurrent miocardialinfarction, etcetera, etcetera.

On the other hand, there may be people who are harmed by taking medicine they don't really need or that are inappropriate, and how we line our way between those two people, is a very good question.

LINDA BROPHY: Any other questions?

JOHN VILLAUME: My name is John Villaume. I'm from Sanofi Pharmaceutical. I apologize, I've been struggling on how to state this precisely, but I can't. But it touches on, I think, a lot of the recent discussions, and that is concerns, risk benefit evaluation, and especially in the recent controversy about the adverse experience reporting and withdraw of drugs. And I just wondered whether, if there's a problem or a weakness, it's

not so much identifying adverse experience -- I think the FDA does that very rapidly -- but rather it is knowing what to do with them and managing expectations so that you can weigh the risks and the benefits in providing a framework for doing that even for FDA advisory committees, which struggle with that kind of decision-making. I just wondered and would like to ask Dr. Woodcock if you can give us your thoughts on that. Is there an effort to revise labeling to present that better so that you can better understand the benefits of the drug and the risks?

JANET WOODCOCK: I'm glad you asked that question. There are certainly many efforts -- and if anybody wants to chip in, please.

As you know, we recently revised the OTC labeling in conjunction with the industry, and I think that will help consumers understand what's in the products and the benefits and the risks

very well. We're going to try to do a similar effort with the package insert that's intended to communicate with the health professionals. And we're going to have to do that, again, through the rule making. So, it will be quite a long process but we're planning to propose something on the package insert.

But the larger issue is how do we, as health professionals, which many of us in this room are, or manufacturers or people who are in charge of producing or testing or quality controlling medicines, how do we manage that risk and benefit balance all through the life of the product from having it made to having it taken by a patient? And as I said, I think we need to have conversation, and that's all the different parties, about that issue, a better framework.

We will be issuing a report in a while, the FDA, as we have evaluated and looked at this issue, and we have

some ideas for ourselves where we can do better, the FDA can do better. As Dr. Henney said, we only do a part of this. We make sure the risks and benefits are well described and honestly communicated in the label and in the advertising, we hope, and that's our role. And we also make a decision, if the benefits for the population outweigh the risks then we will approve the drug for that population. But once the drug is out there, then it's the nurses and the pharmacists and the prescribers and everyone else is in charge of managing those risks that are described and using that information and making sure that the individual person taking a drug, that the benefits should outweigh the risks. And we know there are risks; and so, we also need to make sure, as health professionals, that the people who take medicine know those risks and are aware of what they are assuming.

It seems like there are many

parts in this whole chain that need to be strengthened and improved to maximize the benefits in drugs and minimize the harm although we know there is going to be harm. So, I hope that, with our report and so forth, we'll start a conversation about this. That's what we hope to do.

NANCY SMITH: I would like to add that we, last summer, started a new website where we're trying to post information about all new products that are approved in consumer-friendly language. This was written following the plain-language guideline and it is designed so that a nonmedical, you know, someone without a medical professional background can understand.

We currently have posted all products that have been approved since January of 1998. There are 35 or 40 products now that are up there. We realize, however, that this website will not be as useful as it could be until we

get enough information on all products, not just the ones approved since 1998. So, we're now beginning an effort and we have determined that the easiest or the best way to go about this is to begin with the most commonly prescribed medications.

So, hopefully, with the next three or four months, we will have information up on the top ten products, and then we will be adding to it, sequentially, as often as we can. Again, the constraints in doing this are time constraints. The information is written by pharmacists within the FDA, it then has to be approved by the medical division that approved the product, it has to be looked over by them, it then goes to DeeDee Mac (ph), and they look it over because they want to make sure that we don't say anything that we would not allow the firm to say about the products.

So, it not only has to be

written, but it has to go through two levels of review so that it is satisfactory to the medical division and to DeeDee Mac, and so, it's a time constraint getting more, but we are trying to get more and more information in consumer-friendly language which should help patients themselves to be able to weigh the risks and benefits for themselves. As Dr. Woodcock said, the agency weighs it on a population basis. For this particular population does the benefit outweigh the risk? But an individual is looking at it from their own prospective and it should help them.

JANET WOODCOCK: Well, I appreciated the thoughts on the over-the-counter switches as everyone knows that the self-care and the ability of people with access to medicine, and it's a real important issue for the population. So, it's been important to me, I know that. Having other barrier, an economic barrier and time barrier to

seeking care in getting an intervention is difficult and it doesn't keep some people from getting important care that they need. And the question is, we have to balance that against the risks of people misusing products, which, of course, occurs in the prescription realm as well as the over-the-counter realm. So, I appreciate the input and we will certainly take that into consideration.

STAN REYNOLDS: Good afternoon. Stan Reynolds from Pennsylvania Department of Healthcare Laboratories.

One of the things that we're occasionally involved in is testing food when it's suspected of causing human illness. And quite often, we get questions from the public when someone says, "I bought 'x' 'y' and 'z', I have concerns about it. Who do I talk to?" And one of things that we find perplexing is that right now, there's sort of niche line between the responsibility of the FDA and the

Department of Agriculture when it comes to foods. And you know we're never really certain on a given food product whether to refer the people to the FDA or the Department of Agriculture.

What we would like to know, do you think, at any time in the near future, you two agencies will get together and come up with some clear scheme as to who is responsible for what; like, say, the Department of Agriculture, unprocessed food, the FDA, processed food, something like that? Because right now, it is really very confusing. I'll leave it to the panel.

SUSAN SETTERBERG: I'll take a more generalized food.

Actually, there is some guidance out there as to who does what. And, generally speaking, if it's poultry, any kind of beef, the meats, other than game meats, it's ours. There gets to be confusion when you're talking about things like pizza that has

pepperoni on it. It depends on how much pepperoni.

But in any case, what I would suggest to help immediately is that anyone who has a complaint about a food could call us through our consumer complaint lines which are at each district, and we will help them through that quagmire. We are always interested if they have a problem and we can help them out. That's the best thing.

There is a lot of discussion right now between USDA and FDA about working together to be real clear about who is going to do what where and making sure that we're not redundant, who is in a particular firm, we have set up memorandum of understanding as to who is going to do what where and, of course, working with the states too. So, that will get clarified more and more as we work on the food safety initiative. We work more closer together all the time, but right now, I would suggest that

folks call the consumer and complaint coordinators and we could work that out for them.

PENNY GILES: One of the questions that you asked us was to come up with ideas on how the FDA can better allocate their resources for the minimize of public risk. And unfortunately, I don't have any great ideas, but I was curious as to what you were thinking on that issue right now. I'm sure there's been internal discussions and I'm curious as to what the FDA thinks those resources should be allocated.

JANET WOODCOCK: Could you tell us your name and affiliation?

PENNY GILES: My name is Penny Giles and I'm with Sheryclau (PH) Corporation.

SUSAN SETTERBERG: Where we think the allocations of our resources should be, that's something we face all the time and we make those judgments almost every single day as we're trying

to decide what area we are going to go look at today, what job we need to do today, where crisis is, a lot of what we've been doing lately is doing some risk-based assessment priority setting within all of our program areas. So, we are attempting to hit the most important things we can in every single program.

I think it has to be -- my opinion is it has to be a distribution with expertise in all areas that we regulate. So, it's hard to pick any one particular place, but it has to be based on the impact on the health and the welfare of the people we service. So, that's not a specific answer, but that's kind of how we look at it.

JANET WOODCOCK: I'd say that, in CDER, we actually have looked at this in some extent. And as I said in my talk, it's very difficult. People are really invested in whatever areas they've been doing as far as their importance and their essentiality to

health and it is very difficult for a regulatory agency to determine the effects of deterrence and how important that is. Because you can always say, well, there are no problems, but, oh, that's because there's this tremendous pressing so, if you cut it back, then it's like speed limits or something. You know, if you enforce the speed limits then there are no wrecks, but then, if you didn't enforce it, you would have more problems. So clearly, I would say that for medicines, most of the most serious problems where there is actually an injury and bodies in the street, shall we say, is out in the use of medicines in the community. That is where the problems are, and people are beginning to see that. I think that the long time -- where drug review took a very long time convinced the intention was focused on the time of review and the lack of speed of review and so forth, and that was the subject of

discussion, but now it's really an issue that is not an issue. So, people are saying, well, these drugs are out there, there are a lot of problems, there are adverse there are medication errors, there are unexpected adverse things of drug interaction. We heard people talking about this on the broadcast.

Now, that's more difficult to deal with because we do not control many of those things directly. Those are things we are just players in; and therefore, it is more difficult to convince people that resources need to be shifted in to those areas. And that has long been my conviction and that is what I think.

MICHAEL UMEN: Michael Umen of Michael Umen Company. Just to reflect back on the priority issues and where the agency ought to focus, I did hear Dr. Henney identify, at the beginning of her presentation, by key areas of focus beginning with -- following the FDAMA

mandates and ending up with aluminates smoking amongst young people, and there were three others in between that I forgot, but at least there is some overall agency directive there. But I've become enamored of some of the polls I've seen on television lately, and in thinking out of the box, when you ask the question of what action is being proposed to enable FDA and its products. Centers to focus resources on areas of greatest risk to the public health, I might say, why don't we ask them? Why don't we iteratively consider some polling? Because I know we, as health care professionals seem to think we know, but a lot of the way things get misused or used, some kind of escape our greatest guesses. So, some way of asking them might be one way I proposed. And I don't know what specific way, but let's ask them.

Another comment I'd offer just in thinking about what I've heard today

and reflecting on another one of the questions specifically about what action to be proposed for education of the public about the concept of balancing risk against benefits and public health decision-making.

I've been involved in the drug development approval business for about 25 years and I haven't seen too many drugs that have been approved that have been slam dunk no-brainers, this one is absolutely a clean winner, no risks benefits glaringly outweighing any perceptible risk. They're often very fine lines, and that causes some of their business uncertainty and it also causes some of the uncertainties they think that the public thinks. So, I think the public needs to be clearly made more aware of the reality of this.

I've been impressed by my mother-in-law, who always asks me, "did you read this or did you read that?" She asked me, about ten years ago, "did

you read The Strong Medicine?" That was a pretty eye-opening account of one novelists view of how drugs get developed and misapproved. She then asked me to read Miracle Cure, which was another very interesting one. And then she asked me if I saw a particular episode of Quincy, and at the time that Tourette's syndrome was being raised to the level of interest and it was -- actually, it went to the drug regulations. So, I think we need a good movie and some very good television documentaries that are in a high level of visibility to put the reality into some perspective because I think the public has a really generally misunderstood perspective that everything is absolutely safe and absolutely is going to work on everybody, but that's just not the reality and I think high visibility approaches, media directed may be not within the FDA's budget but, may be

what's necessary.

NANCY SMITH: We've been thinking about a lot of these issues. And back to your first question about polling people, one of the things we've been thinking about lately is trying to do a survey to really determine where people get their medical information. Do they get it, as physicians hope, I guess, from talking with their health care providers and their physicians, or do they get it from TV shows and books that they read? And I think, again, in doing any sort of -- I'm a statistician in my background -- in doing any sort of logical, correct sampling procedure is going to be quite expensive. And I think, if we're going to do this, we need to do it right so that we can be confident in the results. But I think, in this day of managed care when physicians' time is limited to such a short period that they can spend on the patient, they don't have time to go into

the details that maybe the family physician did 50 years ago. And we have to figure out where people are getting their information and the areas where we could make a difference, where we could get unbiased information. I think many physicians get their information about the products from the detailed people that come around from the pharmaceutical companies. And while I certainly would never say that that's misleading, it's certainly not completely unbiased, I think we can all see. And physicians that are so very busy don't have time to weigh the differences between several products that they might prescribe for a particular individual, so they often take the last one they've heard -- you know, prescribe the last one they heard about or something of this nature. So, we need to really find out, not just for the consumers about how they get their information but also from all the health care providers so that we can do a

better job of educating all of them.

LINDA BROPHY: Any other questions?

TOM KIRSCH: My name is Tom Kirsch. I'm from Johnson & Johnson. I have a comment and then perhaps a question.

We heard earlier one of the presenters challenge the FDA try to live up to a perhaps more intense inspection regimen, and I really have to comment about that because, over the last eight or nine years, FDA introduced a process called a Preapproval Inspection Process. And within my own company, over that eight-year period, we would have had perhaps four FDA inspections, if we look at a usual every-two-year kind of surveillance program. In actuality, we've had over 50 preapproval inspections, and I wanted to make sure that the record reflected that. And this has probably consumed maybe a hundred fifty to two hundred days of

inspection time which heretofore would have been -- if you would have thought of a GNP or surveillance inspection of being approximately five days or perhaps even ten days, it would have been 20 to 40 days of inspection. So, I think that certainly, on behalf of my own experience with my own company -- and we're only one company out of 180 companies at Johnson and Johnson -- we certainly feel that the inspections have been very rigorous. Of course, we're dealing with two district offices that are known to be very rigorous, namely in Philadelphia and the Newark district office.

The other comment that I wanted to ask, and perhaps someone like Doug Ellsworth would maybe want to comment, I'm wondering if the agency has any ideas or any thoughts about why the first-party audit concept has really not caught on, to my knowledge, I mean this is not really continuing to be acted

upon by industry.

DOUGLAS ELLSWORTH: Well, I think, with respect to the first-party audit program, I think the industry didn't really see any advantage to entering into that program, but let me just say one thing. You mentioned the number of preapprovals and how many GNP inspections you already had. We're looking at that whole issue of inspections, the field and seat are you will inspect in looking at how we can do it more effectively and efficiently and drawing an appropriate balance between product specific preapproval type inspections, in general, GNP system inspections. How to do those in the most effective way and incorporate both so we're maybe not in your firm 150 times in one year and that we can rely more on some of the general GNP findings that we have. So, we're working on that. And I think that is probably, for us, in terms of risk-based using our resources

appropriately, the things that we need to do first to get our act you will inspect and make sure we're doing the best we can and then see what we can do with some of these other types of pilots. That's my personal feeling.

PAUL G. KING: Since we've opened Pandora's box, this is Dr. King and I'd like to ask a simple question.

Do you count the PAI inspections as part of the number of inspections you do towards your compliance goals?

DOUGLAS ELLSWORTH: You mean the statutory compliance goals?

PAUL G. KING: Yes.

DOUGLAS ELLSWORTH: Not that I'm aware of, no.

PAUL G. KING: So, again, so what you've said -- you're essentially saying to the public is, if people pay for the inspections which is what the preapprovals are paid by the companies, essentially, as part of the PDUFA

program, you'll inspect them as much as you want. Similarly, if somebody is under a consent decree, you will inspect them like crazy. The rest of the industry, you'd inspect, what, 23 percent this year, and 27 percent last year?

First of all, I only raised the issue of inspection as one of the areas where the agency deliberately doesn't comply with the law. The point I tried to make was not that you do more inspections or whatever, that you do good science, good regulatory compliance. And I don't mean just in the inspection, I mean in the approval process. I can cite many instances by name, if necessary, but just in general, where the agency has approved applications where false tests were submitted or where the product was submitted, where it was only formulated to provide 98 percent of the "label claim" and yet those were approved. So,

I want the good science, I want the people to understand the regulations. That's the key message I've attempted to bring to the agency.

And ,as not a real statistician, but as one who certainly understands statistics, I would hope, that your risk-basing assessment, that you start having people that do, because I see people making decisions on risks that don't really understand statistics and I see statisticians working for the industry deliberately skewing those same statistics to help the agency make the "right" decision. I do mean deliberately. I've been involved in a case where somebody, to get you people to approve a certain weight-filling range for a product, grouped the data until the final dispersion was monomodal and then exhibited that data to you. Of course, you did approve the weight-filling range as part of that new drug application but that resulted in

the patients all getting less product than they thought they were getting based on the label claim. You know that's very interesting when you have agencies driven by quality initiatives.

I see the medical people talking about QSR, I hear the agency starting to talk about quality systems, but I don't see them doing much about it and I see them doing the wrong things. Yes, I think it's great to have -- you need better science. People need to apply better science. They need to understand the science that they're applying and the regulations. So, do it right. And Dr. Woodcock, I want to thank you for not appreciating my comments. At least you heard them.

LINDA BROPHY: Well, at this point, I think we're ready to close our session. I think we've exhausted all of the questions from the audience here.

Thank you for your attention.