FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# MARKETED UNAPPROVED DRUGS WORKSHOP

Tuesday, January 9, 2007

8:30 a.m.

Universities at Shady Grove Conference Center
9640 Gudelsky Drive
Auditorium
Building 1
Rockville, Maryland

PAPER MILL REPORTING
Email: atoigo1@verizon.net
(301) 495-5831

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

**Conference Introduction**

MS. AUTOR: Welcome to the Workshop on Marketed Unapproved Drugs. Thank you very much, everybody, for coming today. We are very happy to see you here, and I know we have folks upstairs in the overflow rooms and we thank you as well and hope the accommodations are good up there.

My name is Deborah Autor. I am the Director of the Office of Compliance in CDER at FDA. My job today in part is to speak to you about the substance of the workshop, but also to be your moderator. So, it will be my privilege momentarily to introduce Dr. von Eschenbach and then Dr. Galson who will speak to you. They will then have to depart, after they are done, but I am very glad that they are able to be here today to spend a few minutes to talk to you about unapproved drugs. Again, once they have concluded, I look forward to talking to you more about the substance of the workshop, as we get deeper and deeper into the approval process for marketed unapproved drugs.

First, it is my privilege to introduce Dr. von Eschenbach. Dr. von Eschenbach was sworn in as the 20th commissioner of the U.S. Food and Drug Administration on December 13th, 2006. As the former Director of the National Cancer Institute at the National Institutes of Health, he is a nationally recognized urologic surgeon and oncologist. He has held several positions at the University of Texas, M.D. Anderson Cancer Treatment Center, in Houston. Dr. von Eschenbach has been a distinguished leader in the field of cancer research and progressive patient care for over 30 years. We are honored that his many accomplishments and vast expertise have brought him here to lead the FDA.

**Opening Remarks**

DR. VON ESCHENBACH: Thank you, Deborah, and good morning, ladies and gentlemen. Let me first of all add my welcome to all of you. We are extremely gratified by your commitment and by your turnout here today to discuss an issue and a problem that is of exceeding importance as it

relates to public health, but one that I know you are deeply invested in and deeply concerned about.

Perhaps it is a little bit intimidating, both for you and for me, to begin this morning and my presentation with that chart up on the wall. I asked Deborah are you going to have that up there while I speak? But I think it really begins the morning for both of us in terms of the importance of why we are here and how I hope this day will proceed, that it will proceed in a way that we will work cooperatively and collaboratively together to find our way through that chart, through that pathway so that we arrive at the end of the day having navigated through a very difficult process but one that will lead us to a much, much better place with regard to public health.

The FDA is seriously committed to resolving the problem of unapproved drugs and it is because the FDA is committed to assuring the patients that they are going to be able to obtain drugs for themselves and their children and their grandchildren not just on the hope that they are

safe but based on the fact that FDA has reviewed the evidence and the labeling that defines the conditions under which that drug is safe and effective. It is our responsibility and our mission to fulfill that commitment to the American people, and I know that is your commitment as well. But together we must find a way to do that.

FDA is committed to the mission of protecting and promoting public health and unapproved drugs can be, and are at times, a significant public health issue because unapproved drugs may not meet modern standards for safety, efficacy, quality and labeling. And, our unapproved drugs initiative is an integral part of our overarching commitment to drug safety and our drug safety initiative. You and I are well aware of how deeply concerned the American people are about the safety of the products that we present to them in the way of dealing with diseases or improving their health.

Our drug safety initiative brings all marketed drugs and prescriptions to the same

standard, and our initiative supports the Department of Health and Human Services' strategic goal of reducing threats to health and the well being of Americans.

Our FDA approval of prescription and over-the-counter drugs is not simply a one-time stamp of approval, but it is really an effort on all of our parts to provide a framework for not just approval but ongoing oversight so that we can constantly update the information about those drugs and help physicians and patients make informed decisions based on the most current understanding of that product's risks and benefits. It is the value added that we believe FDA brings to this process on behalf of the American people.

And, we know that many unapproved drugs are, in fact, very valuable to public health and make important contributions to patient well being. But the fact remains that others do not, or that they may be being used inappropriately. So, we must fulfill our mission and our goal to bring that problem to closure by working together with you to

be able to bring all drugs in alignment with the FDA's approval.

Since the announcement of this initiative many of you, many companies have stepped forward and approached the FDA on being able to get their unapproved products approved, and it is in your interest, as well as our interest and public health, to do so. Rather than working on a piecemeal basis, company by company or drug by drug, what we have wanted to do is to address this problem globally. That is why we are sponsoring this workshop, this educational workshop, to bring us all together to work through many of the issues and many of the challenges that will enable us to bring us to a comprehensive solution for all. It is our commitment at FDA to work with industry to solve this problem.

We are a science-based regulatory agency, but we also intend to be a science-led facilitating agency using the modern tools of science and technology to help us facilitate your ability to bring these products that would enhance and improve

the health of American people to them in a way that assures their safety and their efficacy. We are taking this responsibility quite seriously and not approaching it in a draconian or punitive way but intending to approach it in a facilitating, cooperative way, particularly by taking a risk-based approach to our implementation processes and providing industry with both incentives and education and help to come into alignment.

We issued a compliance policy in June of '06 that outlined our risk-based enforcement approach. It is flexible but it is firm. There is the identification of illegally marketed drugs, prioritization of those drugs based on potential harm and undermining of the drug approval system, and methods for subsequent regulatory follow-up. We expect all unapproved drugs to get the required FDA approval, and to do that as expeditiously as possible.

That is why we are so pleased that you are here so that we can discuss this issue and, most importantly, focus on its solutions and understand

its challenges. FDA staff throughout today will be engaged in a series of presentations to explain the FDA position, our policy, and our practices to help you understand the pathway to success. We are also here to listen, to listen to you and to your concerns and to your challenges. We will not promise you we will do what you tell us, but we will listen. My kids never got the difference!

[Laughter]

We know that many of you would like us to use alternative solutions such as a monograph system for unapproved drugs. We have carefully considered that particular recommendation and looked at this issue and determined that, unfortunately, it is not scientifically or economically feasible. We have reported the findings of that effort and the conclusions we drew on monographs to Congress already. But we will continue to work with you and with industry to facilitate the processes to look for ways of assuring safety and efficacy of marketed products, and continue to seek solutions that will enable

this process to be resolved efficiently and effectively.

We want, and it is my commitment that, as we look at this future of exciting opportunity and promise to both protect and promote the public health, FDA will be a bridge to that future and not a barrier. Working together with companies and stakeholders, we are committed to achieving that goal, particularly by making certain that all marketed drugs have FDA approval without adversely affecting public health, without imposing undue burdens on consumers or patients, or without unnecessarily disrupting patient access to drugs that may provide important public health benefits which you have been so committed to making available to them.

We hope to walk this journey cooperatively and collaboratively. The end and the destination is clear and it is firm, but the way is one that we will discover together and, although it appears intimidating at the outset as displayed on the graph, there is a way forward and a way forward

that the FDA has committed to helping you achieve so that together we fulfill our common goal and our common mission to serve the health and the welfare of those people whose hopes have been placed in us.

I welcome you again. I thank you for your commitment. I appreciate your great concern about many of the issues and challenges ahead, but I look forward to your collaboration and cooperation as FDA works with you to achieve success. Thank you very much.

MS. AUTOR: Thank you, Dr. von Eschenbach, for those important and inspiring words. It is now my honor to introduce Dr. Steven Galson. Rear Admiral Galson was named Director of the Center for Drug Evaluation and Research in July, 2005. He provides leadership for the Center's broad national and international programs and pharmaceutical regulation. Dr. Galson joined FDA in April, 2001 as the CDER Deputy Director after holding senior level position at the Environmental Protection Agency, the Department of Energy where he was Chief Medical Officer, and the Department of Health and

Human Services. Dr. Galson is Board Certified in preventive medicine and public health and occupational medicine and, most importantly, we are honored to have him here at this workshop today.

**Welcome**

DR. GALSON: Good morning. Good morning to everybody in this room here today and to remote people upstairs. Sorry, we couldn't fit all of you in here but we are really gratified to see this great turnout today.

I want to thank Dr. von Eschenbach for those inspiring words. As you know, he was confirmed in the middle of December by the U.S. Senate as the Commissioner of FDA, and this is one of his very first few public appearances since his confirmation. We are particularly pleased that he has agreed to be with us this morning at this auspicious time as the permanent Commissioner of the Food and Drug Administration.

I am really encouraged by the turnout as well. I want to thank you for taking the time to come here to learn about the application process

for marketed unapproved drugs. I want to thank all the agency officials as well who put this workshop together, particularly Dr. Deborah Autor who is the Director of Compliance for CDER. She and her colleagues are dedicated to ensuring that drugs in this country are safe, effective and appropriately labeled and correctly manufactured. Their dedication shows in this excellent presentation. We have some of the top leaders from CDER who are going to be here talking to you today, and I know that when you leave at the end of the day you will know a lot more than you know now.

The reason that we are here today is that the agency has significant public health concerns about marketed unapproved drugs. These drugs may not meet modern standards for safety, efficacy, quality or labeling. Tackling the problem that this represents is integral to the comprehensive drug safety strategy that we announced in 2005. It is also an important part of achieving the mission of CDER, which is assuring that safe and effective drugs are available to the U.S. public.

While the U.S. drug regulatory system is widely recognized for bringing these drugs to the market, there are still products that continue to be marketed illegally without documented safety and efficacy information that is required for FDA approval. The public doesn't have a very good understanding of this. When I speak around the country to different audiences, people are amazed to hear that, by some estimates, two percent of all prescriptions are for unapproved products, and what I hear is that they are amazed in a negative way, not in a positive way. What I have heard over and over is that Americans expect their drug products to be approved by the FDA. They don't want products from the dinosaur age of drug regulation; they want products that meet modern standards of safety, efficacy and manufacturing.

We have also heard that healthcare payer organizations don't want to pay for unapproved drugs anymore than consumers want to take them. As our information systems improve it is going to become increasingly easy for payers and consumers

to know which drugs are FDA approved and which are not. We are already passing significant amounts of this information on to CMS [Center for Medicare and Medicaid Services], information that they use in coverage decisions and this sort of information exchange will only grow.

As we announced in June when we published the Compliance Policy Guide for marketed unapproved drugs, FDA has a renewed emphasis on making sure that all drugs have the approval that we are talking about and my hope today is that the presence of so many pharmaceutical manufacturers means that you are interested as well in meeting together with us to address this issue. We are fully prepared to take all the necessary enforcement actions to tackle this problem. In fact, we intend to accelerate these activities in the coming year. But we are equally convinced that it is in the best interests of American consumers, the industry and FDA for companies to voluntarily come into compliance with the law rather than be forced to do so, and I hope that your attendance

today means that you agree with this conclusion. I also hope that the many lawyers and consultants in the audience are here because they want to be part of the cleaning up of this process. If this is so, you will be glad that you are here today because you will learn a lot.

The intended outcome of our workshop today is to make progress towards the goal of having all of these drugs approved or in compliance with the OTC monographs through our combined efforts and continued collaboration. Our mutual efforts to reach this goal will improve the quality of healthcare for all of us by ensuring that the drug products available on the market will be of the highest quality and meet the contemporary standards. Bringing these unapproved drugs under application also ensures the appropriate ongoing oversight of the products. FDA's approval of drugs is more than just a one-time stamp of approval; it is a framework for ongoing oversight to ensure safety and efficacy through the post-marketing period, as all of you know, and to help patients

make informed decisions based on up-to-date information.

You will hear today about the various ways that a drug can be legally marketed, as you have seen the chart. Among the things you will hear about is OTC products, the abbreviated new drug application process and how to demonstrate safety and effectiveness for totally new drugs. You will also hear from authorities about the parameters of the unapproved universe, and this can be very complicated to people--chemistry, manufacturing control requirements for applications, pediatric considerations, exclusivities, user fees, waivers, as well as the role of the Center's unapproved drugs coordinator.

Getting an application approved I would not characterize as being easy, but it is also not necessarily an insurmountable obstacle. We hope that by the end of the day, drug firms, you will see that there is a better path forward than awaiting FDA enforcement. We hope also that we will be providing incentives to companies to come

in and get approval by taking enforcement action against their unapproved competitors, something that I know you all have heard about already.

There is one thing you won't hear us discuss, and Dr. von Eschenbach mentioned it briefly, and that is monographs for prescription drugs. FDA has spent some time carefully considering this and, as many of you know, has provided a report to Congress and we just concluded that a monograph system for the old prescription drugs would be scientifically unfeasible. It is true that we have been able to do monographs for OTC products but prescription drugs are different. As compared to OTC drugs, the labeling for prescription drugs is much more detailed and less able to be generalized to a class. The risks of many prescription drugs are also much higher than for OTC drugs. That is why they are prescription. So, the risks and benefits of each drug really have to be considered separately. As well, the chemistry, manufacturing and bioavailability of prescription drugs are critical to their safe and

effective use and must be evaluated on an individual product basis.

We also found that a monograph system for prescription drugs would take many, many years to implement and would be cost prohibitive. We estimate that developing and implementing a monograph system for many of the currently unapproved prescription drugs would cost the government up to three hundred million dollars over a ten-year period, and that is simply not an acceptable number and period of time. So, writing monographs is just not a viable option.

We have a lot of material on the agenda for the day. Again, our primary intention is to provide clarification and direction to industry on how to legally market drugs through the OTC monograph, NDA and ANDA process. I know you will have a better understanding of all these issues by the end of the day. We hope as well that you will come away with an understanding of the appropriate agency contacts so you know actually what to do next as you work through the application process.

Once again, thank you very much for being here. I wish you all a fruitful and productive day and welcome.

**Overview of the "Unapproved Universe"**

MS. AUTOR: Thank you, Dr. Galson, for those very informative words. We really appreciate his presence today and again, of course, having Dr. von Eschenbach here was also an honor and a real contribution.

I am going to cover four things this morning. I am going to talk first of all about why FDA is concerned about unapproved drugs. You have heard both Dr. Galson and Dr. von Eschenbach allude to that. I will go into a little bit more detail just so you have an understanding of our view point on that.

I will then talk about a legal description of the unapproved universe. The idea of that is to create some common understanding as well as some common vocabulary, containing such words as DESI and GRAS/GRAE, terms a lot of you probably already know but, hopefully, by the end of the day we will

have the same definitions of those.

We will then talk about the unapproved drugs initiative, the 2006 CPG, the Compliance Policy Guide for Marketed Unapproved Drugs which you heard about already today, as well as the multi-pronged approach that the agency has adopted for tackling the unapproved drugs problem. Again, you have heard a little bit about that today but I will just cover that one last time. Then, an overview of the workshop. I will tell you in a minute about the agenda but I think the workshop will shift gears a little bit when I am done. I think we are going to really turn to the serious educational focus and talk to you about how to get through the approval process.

So, I want to talk first about why FDA is concerned about unapproved drugs. First, physicians and consumers cannot assume that marketed drugs have been found by FDA to be safe and effective. This is true even if those drugs are listed in the Physician's Desk Reference, advertised in trade journals or brought into

physicians' offices by drug firm sales reps.

There is also no label review of these drugs. This is inconsistent with the agency's current approach to drug safety. We try to advise physicians and consumers of emerging risks so that they can make the best possible medical decisions. In this case physicians are unaware that the drugs that they are taking or giving to their patients are non-FDA approved, and they are making their decisions based on drug labels that have not been reviewed by FDA and do not reflect the latest scientific knowledge, literature and adverse event findings.

Just to give you a couple of examples, in June of last year, as you probably know, we took action against marketed unapproved carbinoxamine products. This is a sedating antihistamine which was labeled for children down to one month of age which we did not think was appropriate. Moreover, there were different versions of the drug with the same name. Some of them contain carbinoxamine alone; some of them contain carbinoxamine and

pseudoephedrine-again labeled for babies. That is not an appropriate public health situation.

We have also found unapproved drugs where there is an approved version that has a black box warning, FDA's most severe warning about a side effect of the drug, and unapproved versions with no warning. Again, this is really a cause for concern for us.

There is also an increased risk of drug quality deficiencies. There is no FDA review of the chemistry, manufacturing and controls for these products. There is no review for the specifications and there is no pre-approval inspection.

There is limited post-market surveillance and no periodic reporting. There is no annual report. The adverse event reporting requirements for unapproved drugs are relatively new and limited. Now, I grant you that in some cases there may not be a documented risk but the absence of proof of a problem is not proof of the absence of a problem. Adverse reporting data are limited. Many

adverse events are not identified or, if they are identified, are not reported. We cannot assume that an unapproved prescription drug is safe or effective simply because it has been marketed for some period of time without identification of serious safety or effectiveness problems.

Finally, these drugs challenge the integrity of the drug approval system. They reduce incentives for research to prove safety and effectiveness, and they create an inequitable situation where unapproved drugs compete unfairly with approved ones.

Now let me talk a little bit about the definition of the unapproved universe. As Dr. Galson said, FDA estimates that there are several thousand illegal, marketed unapproved drugs today. This very rough estimate is comprised of several hundred drugs, several hundred different active ingredients in various strengths, combinations and dosage forms from multiple distributors and repackagers. FDA estimates that this is approximately two percent of all prescriptions

written per year in the U.S., again, very roughly. There are three main categories of marketed unapproved drugs: DESI drugs not under an application, prescription "wrap-up" drugs, and post 1962 drugs.

I am going to talk a little bit about what that means for some of you. This may be something you already know well. For some of you it may not be something you know as well. First, DESI. In 1962 Congress amended the Federal Food, Drug and Cosmetic Act to require that new drugs be proven effective as well as safe to obtain FDA approval. This amendment also required FDA to conduct an evaluation of the effectiveness of the drug products that the agency had approved as safe between 1938 and 1962. This review is called the Drug Efficacy Study Implementation, or DESI.

DESI is largely completed. The unapproved universe DESI drugs that we are talking about today are those that are subject to already completed DESI proceedings or those that are identical, related or similar to them but lack required

applications. These may be products for which there is a DESI determination of a lack of substantial evidence of effectiveness or a final determination that the product is effective, but in either case there is a final order that requires FDA approval but applications have not been submitted and approved as required. These products are marketed illegally. DESI drugs are not grandfathered and are not GRAS/GRAE. Those are different words so we need to make sure we are talking about different things. DESI, again, is the Drug Efficacy Study Implementation review for efficacy of pre-'62 approved drugs.

The second category in the unapproved universe is prescription drug "wrap-up" drugs. These are pre-1962 non-DESI marketed drug products. Many drugs came on the market before 1962 without FDA approval. Drugs that did not have pre-1962 approvals were not subject to DESI if they were not identical, related or similar to a DESI drug. Many of these drugs claim to have been marketed prior to 1938 or to be identical or related or similar to a

pre-1938 drug and, therefore, to be grandfathered. But a prescription drug "wrap-up" drug is marketed illegally unless the manufacturer of such a drug can establish that his drug was grandfathered or otherwise not a new drug, which we believe is unlikely and I will get into that a little bit more in a minute.

Then, there are new unapproved drugs. Some unapproved drugs had first been marketed or changed after 1962. These drugs are also on the market illegally. In some cases these drugs may already be subject to a formal agency finding that they are new drugs that need FDA approval such as for the post-1962 extended release products. Now all extended release products are subject to that finding, but there are post-'62 drugs that came on the market and are still subject to that finding. They are extended-release drugs, therefore, they need FDA approval.

The bottom line for unapproved drugs is that all drugs must have FDA approval or comply with an OTC, over-the-counter, monograph unless

they are DESI pending or OTC monograph pending. That is the first situation. But there are less than 20 DESI proceedings currently pending out of almost 600. There are not a lot of DESI pending proceedings or DESI pending drugs remaining. And, many of the OTC monographs have been finalized so that is also not that big a category. We strongly recommend that a firm review FDA's website on the rulemaking history for non-prescription drugs to learn whether proposed or marketed OTC drugs are in compliance with the regulations.

The second reason that a drug might not need FDA approval is if it generally recognized as safe and effective. The agency believes that it is not likely that any currently marketed prescription drug is GRAS/GRAE. For example, a GRAS/GRAE finding requires a consensus among experts that the product is safe and effective based on published scientific literature regarding that finished drug product. The literature must be of the same quality and quantity that would be required to approve a drug under section 505 of the Federal

Food, Drug and Cosmetic Act. That is a very high standard.

Finally the third reason-I think I said there are four but there are three, the third reason that a drug might not require FDA approval would be if it is grandfathered. The agency believes that it is not likely that any currently marketed prescription drug is grandfathered. For example, for grandfather status a firm must document that its product is identical in formulation, strength, dosage form, route of administration, indications, intended patient population and other conditions of use to a drug marketed on the relevant date for the 1938 or 1962 grandfather clause. For the 1962 grandfather clause, the firm must also document that the drug was GRAS, generally recognized as safe, in 1962 based on published scientific literature.

Now, this workshop is not going to be about GRAS/GRAE, grandfather and enforcing those standards. That is really beyond the scope of this workshop. If you have questions about it you are

welcome to address them to my office, the Office of Compliance. We really would like to spend the time today talking about the approval process. Let me go briefly over the goals of the 2006 CPG just to make sure, again, that we are all sort of starting from the same place.

The goals of the 2006 CPG are to improve the safety of the drug supply by enforcement and by bolstering incentives to submit applications for marketed unapproved drugs. We want to encourage companies to comply with the drug approval process while minimizing disruption to the marketplace. At the same time however, and I think Dr. von Eschenbach and Dr. Galson were clear on this, we want to provide notice that any product that is being marketed illegally is subject to FDA enforcement at any time.

We talked in the CPG about our enforcement priorities. These priorities apply equally to all unapproved drugs, whether they are DESI, "wrap-up" or post-'62 drugs. Our priorities are drugs with potential safety risks because, first and foremost,

we are here to protect the public health; drugs that lack evidence of effectiveness; fraudulent drugs; unapproved drugs that directly compete with an approved drug; drugs from manufacturers that are otherwise violating the Act, for example, manufacturers that have GMP violations or ADE reporting violations at their firms, and drugs with formulation changes made as a pretext to avoid enforcement such as changes made for the purpose of distinguishing the drug from an approved product with which it competes.

Now, I don't want to give you the wrong impression. We are not going to go and do all of the priority one drugs, followed by all the priority two drugs, followed by all the priority three drugs because we would be prioritizing for the next 50 years and that is not what this is about. These are all our priorities and, as we said, any drug at this point could be a target of an enforcement action. We will, of course, look at those factors in considering which action to take next but I want you to understand that those

priorities all exist simultaneously.

FDA is committed to tackling the unapproved drugs problem and we are doing it through a multi-pronged approach including enforcement. As many of you know, we have already taken multiple enforcement actions ranging from injunction cases to Federal Register notices under the CPG, and we will be considering what kinds of actions to take in the future.

As Dr. Galson said, we are fully prepared to take the necessary enforcement to tackle the unapproved drugs problem. In fact, we do intend to accelerate that enforcement in the coming year, as he mentioned. But we hope that enforcement won't be the only way the problem is resolved. We really do. And, that is why we are here today. We are here today to try to educate you; to try to help you through the approval process so that we can all get to what I hope is our mutual goal, which is to have these drugs approved and have consumers have the assurance of safety and efficacy, good quality and good labeling in the products that we all know

they are entitled to.

The incentives piece is to take action against unapproved versions of a drug where one version gets approval. As I mentioned, that is a priority of ours. And, other measures. Whenever it becomes appropriate we will be looking at all the ways that we can address this issue. We really want companies to decide that proactive compliance is achievable and is in their best interests.

I did allude to one of the reasons why we are having this workshop, which is that we frequently have questions asked by industry about the approval process, and we thought it made sense to try to give everybody some understanding of that and try to answer a lot of those questions at once so that we can create some common knowledge there. This workshop is a product of the CDER/ORA unapproved drugs working group that meets weekly to talk about this initiative and to further this initiative and take action. Our intent is to educate, especially small businesses, and we hope that with education and incentives companies will

take the initiative to get approval, and enforcement will be necessary in fewer cases.

As Dr. Galson mentioned, we have had a lot of calls since the publication of the final CPG with people wanting to understand the approval process. We have had over 40 calls from firms and representatives requesting information about the approval process. Firms have filed INDs to begin clinical trials of previously unapproved drugs and firms have identified commonly marketed unapproved drugs and requested meetings to discuss what they need to do to get approval for those drugs.

So, here we are today. Obviously, with respect to specific drugs-you will hear more about this today but with respect to specific drugs, CDER is willing to sit down with manufacturers and discuss the specifics of the approval process for those drugs, but there are a lot of general questions that we thought could be addressed for everybody.

We will, of course, have to talk in generalities. There is only so much we can do in

one day so we will only be able to give some general guidance but we really think that today will be productive and you will learn a lot. You can address specific scientific questions after the fact to the relevant division of the Office of New Drugs and, at the end of the day Sally Loewke, who is our unapproved drugs coordinator, will tell you more about that. You can address legal questions to my office, the Office of Compliance.

I will run quickly through the agenda. Dr. Galson really covered this. We will talk about the regulatory pathways for legal marketing; OTC monographs; ANDAs; 505(b)(1) and 505(b)(2) NDAs and I think if these are terms you don't understand, you will understand them better by the end of the day; and other important issues for applicants such as chemistry, manufacturing and controls; pediatric considerations; exclusivities; user fees and waivers; and the role of the unapproved drugs coordinator.

One thing to keep in mind as you listen today, because I think this is something that will

be on the minds of a lot of the speakers, is that there is a range of drugs that we are talking about, sort of a spectrum of uncertainty. Some of these drugs are active ingredients that are unknown. At least from FDA's regulatory standpoint, we have never dealt with them so we don't have information about their safety and effectiveness. We don't have an understanding of that. A new molecule, never previously approved, is an example of that.

Some of these drugs are well-known active ingredients, situations where a drug has already been approved for another firm or the drug has already gone through the DESI process and been found to be effective. So, I think as you listen today you will need to think in your minds where your drugs fall in that spectrum and how what you are hearing relates then to your specific products.

I have to talk briefly about the decision tree that you all have copies of and which Dr. von Eschenbach had some fun with. That is intended to be a guide. It is frankly a big effort by the

agency to clarify some pretty complex issues. Mike Folkendt, who is sitting here today from the Office of New Drug Quality Assessment, deserves a medal because he was drafted and spent hours and hours and hours trying to perfect that document for you, and we really hope it is helpful. I can't guarantee it is perfect but it really is intended to be a guide as you start to learn more about the different ways to legally market a drug and help you to figure out where you drug falls within that. It probably doesn't look crystal clear now and it may not be crystal clear by the end of the day but we hope you will have a better understanding of what it means and how it works.

Finally just to wrap up, again as I said, we can only really brush the surface today, but we really do hope that this workshop will help manufacturers of unapproved drugs to understand how to comply with the law. After the workshop we will post the slides that are up there now but people change their slides with post-final slides, and we also intend to build an education section on our

unapproved drugs web page. For those of you who haven't seen the web page, that is the URL for it up there, but we will build an education section which should have links to relevant guidances and other web pages that might be helpful.

Thank you again for coming today, and it is now my pleasure to introduce the next speaker, stepping back into my role as the moderator. Let me say to folks here I think there is more overflow space in room 102. If anybody wants to go, there are desks and there is a video feed. So, if you feel you would be more comfortable, please feel free. If not, of course, we are happy to have you here as well.

Again, thank you. It is now my pleasure to introduce Dr. Reynold Tan. Dr. Tan is an interdisciplinary scientist in the Office of Nonprescription Products. Dr. Tan received his Bachelor's Degree in biochemistry from the University of Pennsylvania and Ph.D. in biochemistry from the University of Maryland. Prior to coming to FDA he worked for five years as

a research chemist for Knoll Pharmaceutical Company. Dr. Tan has been an interdisciplinary scientist in the Office of Nonprescription Products at FDA since 2002 and he is among our many very distinguished and very well versed speakers today. He will be talking about the regulatory pathway for OTC monographs.

**Regulatory Pathway: OTC Monographs**

DR. TAN: Good morning. I am Reynold Tan. I was just reflecting that I am one of those people that came over from industry to FDA so I actually really appreciate this opportunity to talk about this today because the information you are getting today is exactly the kind of information, while I worked in industry, that was the information I really wanted to get. But in starting our talk about regulatory pathways, talking about this OTC monograph regulatory pathway, the OTC monograph regulatory pathway is one pathway by which we regulate OTC drugs. The other pathway is the NDA pathway and that is going to be discussed later.

So, just to emphasize, I am talking about OTC drug regulation, and by OTC drugs I am talking about over-the-counter drugs or nonprescription drugs. Prior to 1951, in fact, manufacturers could promote their drugs as either prescription or OTC. So it wasn't until 1951 that the Durham Humphrey Amendment to the Food, Drug and Cosmetic Act authorized FDA to classify certain drugs as available by prescription only. Those drugs that remained OTC are drugs that FDA believes can be used safely and effectively by the labeled information without the intervention of a healthcare provider.

OTC drugs are regulated by our Office of Nonprescription Products. That is the office I work for. There is our general office website. You can go there and find out who we are and what we do, and it has links to most of the other information that I am going to be covering in my talk.

Important to understanding the regulation of OTC drugs is noting that there are two

regulatory pathways by which we regulate OTCs. These pathways are the new drug application pathway and the OTC drug monograph pathway. The main difference between these pathways is that for the new drug application FDA approves marketing. That is based on data and information for safety and effectiveness that you, the manufacturer, submits to us for your specific drug product.

That is not the case for the OTC monograph. With the monograph we allow marketing as long as your product complies with established required conditions for safety and effectiveness. We establish these required conditions per drug category, per OTC drug category and the active ingredients in that OTC drug category.

So, I am just talking about the OTC drug monograph. NDAs are later so I am going to fade out the NDA pathway. The OTC drug monographs are created or developed through the OTC Drug Review so I am going to be talking about the OTC Drug Review as well.

First a general description of what an OTC

drug monograph is, it is sometimes referred to as a recipe book for manufacturing or marketing an OTC drug product. Just like following a recipe, if you follow the steps in an OTC monograph you come up with the desired product. For an OTC monograph, that desired product is what we term a GRASE, or generally recognized as safe and effective, product. I need to emphasize here that when I speak about the term GRASE here, it is specific to the OTC monograph process. That is not the GRASE that Deb Autor just mentioned.

The monograph actually lists the required GRASE conditions which, if followed, end up with a GRASE product which complies with the monograph. Each final monograph-and, again, there is a final monograph for each OTC drug category, is published in the Code of Federal Regulations. For example, if you go to 21 CFR Part 331 you will actually find the final monograph for OTC antacid products. Part 332 is the final monograph for OTC antiflatulant products, and so forth. Some monographs are still in the proposed stage so you will see gaps in that

numbering sequence. You can find both the final and proposed monographs at the industry website shown here.

More about these required GRASE conditions or conditions of use are listed in the OTC drug monograph. Each monograph starts out with the allowed active ingredients and includes required dosage strength and sometimes we have requirements for dosage form. Following that, there are labeling requirements. So, you need to use specific language for your indications, warnings and directions statement although you have some flexibility in your indications statement. Sometimes, as well, we have final formulation testing.

The decision tree. Unfortunately, if you printed out the draft slides, this will differ a little bit from the printout because we really worked on this decision tree and we tried to make it accommodate every situation. But I am going to use it as a guide through my talk and I am going to be covering the yellow branches of the tree which

can end up at the middle column and the bottom left diamond and oval. Those are the OTC monograph branches of the tree. I will track progress through those branches using that red arrow.

So, let's start with the top center decision point. This is a fairly important decision point and it is fairly restrictive. At this point you need to determine if your product's ingredient, strength, dosage form, route of administration, directions, etc., taken as a whole are reviewed under the OTC Drug Review. To explain that I will now do some slides that show what is reviewed under the OTC Drug Review.

There is an overview of the OTC Drug Review in 21 CFR part 330. To understand the OTC Drug Review you have to go back to 1972, when it began and understand that in the early '70s there were anywhere between 100,000 to 500,000 marketed OTC products so it was not feasible to do a product-by-product review of all these products. However, FDA estimated that these products contained as few as 200 OTC active ingredients and

approximately 26 OTC drug categories. So, the idea was to do a safety and effectiveness review of the active ingredients per OTC drug category and create monographs for each drug category. To find out which active ingredients and the drug categories in which they were reviewed under the OTC Drug Review, you can see the OTC Drug Review ingredients status report also at the industry website.

OTC monographs are developed through the OTC Drug Review. Each OTC monograph, again representing an OTC drug category, is developed through a three-step public rulemaking process. Each of these three steps involves the publication of a document in the Federal Register. These three documents are the advance notice of proposed rulemaking. That is followed by a tentative final monograph, or TFM, and finally the final monograph, the FM. So, the intent of this three-step public rulemaking process was to allow comment periods after each of the proposed monographs so after the ANPR and the TFM, that is, preceding our final conclusions in the final monograph. The comments

to the proposed monographs can be found as dockets submissions at our public dockets website. That is shown there. You can check the status of each monograph at the second website shown there.

The next few slides will step through the three-step process for developing a monograph. Again, back in the '70s when we formed advisory review panels, these panels were charged with reviewing OTC products that were on the market at that time. They were charged with looking at the active ingredients in these OTC products, and they were to categorize the safety and effectiveness into three categories. Category I active ingredients are those active ingredients for which the available data for those active ingredients showed that they were safe and effective. Category II is the opposite. The available data for those active ingredients showed that the active ingredient was not safe and effective. For category III the available data for the active ingredient was inadequate to determine safety and effectiveness. Again, this is for the particular

drug category of the monograph.

The panels' categorization for safety and effectiveness of each active ingredient and their labeled recommendations are published in that first document, the ANPR. Publication of the ANPR opens up a 90-day comment period. FDA reviews those comments and, if the comment is valid, we revise the proposed monograph in the ANPR and publish a tentative final monograph.

This tentative final monograph opens up the second 90-day comment period and a one-year period for submitting additional data. We look at these submissions and, again, we revise the proposed monograph if it is appropriate and we publish our conclusions in the final monograph.

The final monograph, like the TFM, includes a discussion of the reasoning behind coming up with our conclusions in the monograph. The final monograph also has an effective date by which manufacturers have to comply with the conditions.

Back to the decision tree. I have just

discussed the product review under the OTC Drug Review. At this point, if your product still remains in the monograph pathway your next branch point is to determine whether your product's indication is the same or different than that reviewed under the OTC Drug Review. If it is the same and not different, then your next branch point is to determine whether the monograph applicable to your product is final or has not yet been made final. If your product has an applicable monograph that is final and it complies with the specifications in the final monograph, then you can legally market it under the final monograph. So, I am going to provide an example of that.

Here, on the left is the first page of the antacid final monograph as it appears in the CFR. On the right you see the Drug Facts label for a product that complies with the final monograph. The antacid final monograph, again like all monographs, starts with the allowed active ingredients. One of the allowed active ingredients for antacids is calcium carbonate. You can see

that the Drug Facts label is labeled in compliance.

The required indication statement in the antacid FM states "for the relief of (optional, any or all of the following) heartburn, sour stomach and/or acid indigestion." You can see that this indication statement does, in fact, appear in the label.

An example of following the warnings requirement, one of the warnings must be "do not take more than (maximum recommended daily dosage) in a 24-hour period, or use the maximum dosage of this product for more than 2 weeks." And, that does appear in the label.

So, this process of complying with each of the requirements in the final monograph lets this product comply with the final monograph and can be legally marketed. You also should note that your product has to follow the Drug Facts format in labeling.

Back to the decision tree, and now we are going to cover this branch and this is if your product has an applicable monograph but that

monograph has not yet been made final so it is at the ANPR stage or the TFM stage.

If the ingredient and indication are, one, under the OTC Drug Review, and they must be at this point in the decision tree and, two, they are not in the final monograph, then the ingredient and its indication can be marketed pending completion of the final monograph.

The compliance policy guide, Sections 450.200 and 450.300 state our policy under this situation. It includes this statement, we are unlikely to pursue regulatory action unless your product poses a potential health hazard to the consumer. There is the link to the compliance policy guide. Regulations in 21 CFR 330.13 cover conditions for marketing ingredients recommended for OTC use under the OTC Drug Review. This also contains a cautionary statement that continued marketing is at risk that the proposed conditions, the proposed GRASE conditions, in the proposed monograph may change.

There are important exceptions to

marketing using an ongoing monograph procedure or under an ongoing monograph procedure. So, in 21 CFR 310 sections 500 there is a list of drug products that are categorically considered new drugs. In other words, these products cannot be marketed under the OTC monograph pathway. They require NDAs. For example, 21 CFR 310.545 lists specific active ingredients in specific OTC drug categories that are not GRASE for OTC drug products. If your product contains one of these listed active ingredients you can't market under the OTC monograph. 21 CFR 310.502(a)(14) states that time-released dosage forms are categorically considered new drugs. For example, cough/cold extended-release products that are marketed OTC are not legally marketed under the monograph pathway. 21 CFR 310.503 similarly states that irradiated drug products are new drugs.

**Comment [t1]:** I got the section wrong here. It should be 310.502(a)(12): "Drugs sterilized by irradiation"

I have essentially covered the yellow branches or the monograph branches of the tree. I have discussed how, if your product has an applicable monograph that is final and your product

complies with the final monograph you can market. Now I am going to talk about mechanisms if your product deviates slightly from the final monograph. Marketing a drug product that deviates from a final monograph can be pursued using the NDA deviation mechanism or the citizen petition mechanism. These mechanisms actually make use of the final monograph, as I will show now.

First I will do the NDA deviation. The regulations for the NDA deviation are in 21 CFR 330.11 and it is more accurately termed a monograph deviation because what it is, it is an NDA 505(b)(2) application that references a final monograph. This mechanism is appropriate if your product meets all conditions of the applicable final monograph except for a deviation. In essence, it is deviating from a monograph, not deviating from an approved NDA. Your NDA deviation application must include data to support the safety and effectiveness of your product with the deviation.

Now I will provide an example of that. A

manufacturer of a pyrethrin plus piperonyl butoxide aerosol foam wanted to market their product as an OTC pediculicide but the final monograph for OTC pediculicides only allows this combination in a non-aerosol dosage form. So, the manufacturer contended that their product meets all the conditions of the pediculicide final monograph except for this deviation in the dosage form. They referenced safety and effectiveness information in the pediculicide final monograph, then they submitted additional bridging type studies linking the safety and effectiveness of their product, the aerosol foam, to the similar monograph product which is non-aerosol dosage forms, and they submitted new chemistry, manufacturing and control information. FDA approved this NDA deviation application based on both the data submitted in the NDA deviation application and data information in the pediculicide final monograph.

The citizen petition is the second mechanism that you can use if your product deviates slightly from the final monograph. The regulations

are in 21 CFR 10.30. It can be used to amend the OTC monograph at any step of the monograph process, not just the final monograph but TFM and any proposed monograph. The important stipulation is that the citizen petition is limited to pre-1975 marketing conditions so you can only use it if your product was marketed before 1975 or, in other words, marketed before the OTC Drug Review began. It can be used for a pre-'75 product or any of the product's conditions. By conditions, I mean the active ingredient, dosage form, indication, etc. The citizen petition must include data or information demonstrating safety and effectiveness, and you can't market the product with the new condition until the final monograph is ultimately amended.

Lastly, there are two mechanisms that allow you to become eligible for the OTC Drug Review which I have depicted here by the mechanisms feeding back into the top of the branch. I have just discussed the citizen petition. Now I am going to talk about the time and extent

application.

The time and extent application is a mechanism to incorporate a new product or a product condition into a monograph. The regulations are found in 21 CFR 330.14. It can be used to amend the OTC drug monograph at any step in the monograph process. It can be used for OTC drugs marketed in the U.S. after 1975, importantly, under an approved NDA but more commonly it is used for OTC drugs with marketing experience outside the United States or foreign marketing experience.

It is a two-step process. Step one is an eligibility step. You need to show that your product meets marketing requirements for being marketed for material time and material extent, which are described in 21 CFR 330.14(b). By material time we generally mean that you have to show that your product was marketed for greater than five continuous years in the same country. A requirement for being marketed to a material extent is described as being marketed in sufficient quantity. That has to be assessed for each

specific product.

If you complete the step for eligibility, then you still need to complete a second step for safety and effectiveness. FDA conducts this review for safety and effectiveness in the same manner that it conducts the safety and effectiveness review under the OTC Drug Review.

Here is an example of a time and extent application that actually completed step one for eligibility. It is a manufacturer of a dandruff shampoo containing climbazole. That manufacturer wanted climbazole included in the dandruff final monograph. The problem is that the dandruff final monograph doesn't allow climbazole currently. So, the manufacturer submitted a request for TEA eligibility that included data information on its foreign marketing experience. This information showed that the product was marketed to a diverse population representative of the U.S. population and also that marketing in foreign countries was marketed in an OTC-like environment. Their application also included marketing data on the

number of dosage units sold.

FDA concluded that TEA eligibility was demonstrated and we published a notice of eligibility and call-for-data in the Federal Register. You can reference this document at the website shown here. Importantly, this is just completing the first step of the TEA. It still has to complete that second step for safety and effectiveness so the product cannot be marketed until a final monograph is published. Also importantly, we informed the manufacturer that a USP monograph is required to be established for climbazole. All allowed active ingredients that are in the final monograph actually have to have a USP monograph.

That concludes my talk. I hope you got some helpful information from that. Here are the internet websites that I have referenced in my talk. Also, there are some email contacts there for you for people in our office. We realize these issues can be really complex so these people actually set up meetings where we can actually

resolve these complex issues. Thanks.

MS. AUTOR: Thank you very much, Dr. Tan. I think that was a very helpful overview of the OTC monograph process. Our next speaker is Dr. Moheb Nasr, who is the Director of the Office of New Drug Quality Assessment. ONDQA is responsible for quality assessments of new drugs, pre- and post-marketing, regulated by CDER. Dr. Nasr, among many other illustrious activities, serves as the FDA lead at the International Conference on Harmonization, ICH Q8 expert working group and is a member of FDA's Council on Pharmaceutical Quality. Dr. Nasr joined the FDA in 1990 after a distinguished academic career, and we are very pleased to have him.

**Chemistry, Manufacturing and Controls Requirements**

DR. NASR: Good morning. I think some of you who know me will be relieved that I am providing today only 15 or 16 slides. I always have about a hundred or so slides. My presentation today will focus on providing some of the technical information needed to meet our application

expectations as far as chemistry, manufacturing and controls.

What I will address today is some general information and references; our expectations, and I am calling that "expectations" rather than "requirements" because some of the regulations may not be clear enough in our expectation and guidelines and approaches and changes over the years so I am trying to share with you what we expect to see as far as manufacturing and quality requirements both for drug substance and drug product. I would like also to provide you with some additional considerations for your benefit.

Here are some references and, as Deborah mentioned this morning, all these slides will be available to you all. You will be able to get this information. I will leave you also with some contact information in my office where I can be reached. So, as far as the content of an application, here is the regulation. Here is our website. Some of our internal procedures are outlined in MaPPs. Here is a reference for it.

GMPs, some additional and helpful information as well. So, this is an important reference slide and the information there will be useful as you approach preparing an application for some of your products.

As far as some of the general expectations and requirements for both an abbreviated new drug application and new drug application submission, the format we recommend is the formal technical document formatting but it is not required. You can either go by that in the form of a paper submission or electronic. You can reference the required information in a drug master file or what we call DMF, the DMF reference for drug substance, packaging components and excipients, and you must have an appropriate letter of authorization in order to enable us to access the DMF and review the information there as far as its relevance to the drug application.

For a new drug application, and that is the area where I have some responsibility, we strongly recommend that you meet with us prior to

submission. So, this is an advantage you have in the new drug area. Because some of you may lack the expertise for some of the current requirements and information, we strongly recommend that you meet with us and we will be happy to provide consultation and helpful hints about how you submit and the kind of information we would like to have. Again, I am going to leave you with some specific contact information.

As far as CMC expectations in general, and this applies to both new drugs and generic drugs, if there is some distinction or some differences I will highlight the differences. We will expect a full description of the composition, manufacture and specifications as outlined in our regulation. It must include chemistry, manufacturing and controls, and that is what is called CMC. Most of you may call it chemistry requirements. In Europe it is called quality requirements but it is generally chemistry, manufacturing and controls for drug substance, drug product, excipients and packaging components and additional information as

appropriate if you need, for example, to provide information in comparison studies.

Drug substance is the active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, etc. All this information is in the regulation.

What is more specific information that we would like to see as far as the drug substance? We would like to see a full description of the drug substance as far as its identity, physical and chemical characteristics, stability, the method of preparation or manufacturing or synthesis, isolation, purification including appropriate selection of starting material. This is an issue that even today the most sophisticated drug manufacturers have questions about. How can we define our starting material both for regulatory purposes and GMP controls, etc? We usually meet with the sponsors to provide clarity and provide advice on how to establish the starting material.

Manufacturing process controls, if there

is some need for in-process testing, etc. and specifications, and I will provide a little more clarity because there is misunderstanding at times about what we mean by specifications, including the test methods necessary to ensure purity and drug product performance and level and qualification of impurities, and that is important. And, I am providing you here with some of the ICH guidances. ICH, for those who are not as familiar with this particular part of our guidelines, is the International Conference on Harmonization where there is harmonization of quality, efficacy and safety requirements in the three regions, the U.S., Europe and Japan. And, we very much adhere to these guidelines. If there are differences or different regional interpretations we try to explain that.

We need to know the name and address and contact information of the manufacturer. If you reference the drug master file we need to have the appropriate letter of authorization, as I indicated in a pervious slide.

The complexity of drug substance can vary. Some are fairly simple and some are more complex. That complexity can be due to the synthesis process used whether it is chemical or enzymatic; whether it is a single or multi-step or a stereo-specific synthetic scheme related to a particular isomer; whether it is fermentation or recombinant biotechnological methods of manufacturing; whether it is chemically prepared or naturally derived. Also some additional factors affect the complexity of drug substance, namely, some of the physicochemical characteristics, thermal stability and so forth.

We will be talking about drug substance stability for drug product but I will try to highlight the differences. Also, in today's presentations they intend to provide clarity and assistance to encourage you all to prepare your applications. Drug substance stability and information is needed to establish a retest date or expiry assigned based upon data. So, the data have to show that information in order to reach a

regulatory decision. Information is needed about stability testing protocol, stability testing under control conditions, and usually we would like to see stability information for both accelerated conditions, that is, 45 degrees, 75 percent relative humidity, and room temperature, and that is 25, 60 percent relative humidity.

Test and acceptance criteria. This is an area where a good stability indicating assay, most likely a chromatographic analytical method, would be needed to distinguish between the active and some of the potential degradation products, and that is different from some of the very old analytical methods where titration, for example, can be used to assay for the active.

Testing frequency. You can use the background information provided in ICH Q1A. Container closure system representative of large bulk container, drum etc. Here are our submission expectations. Even though this is a fairly busy slide, I am trying to provide the requirements and the differences in our expectation for new drugs

and generic drugs. For new drug applications we expect to see three-batch information; six months of room temperature and accelerated data. We would like some presentation or discussion about how an applicant can statistically project expiry up to six months past the room temperature data. Some discussion on trending or potential trending needs to be provided in the submission.

For an abbreviated drug application, however, you need only to provide information for one batch. So, for an abbreviated drug application you need information only for one batch and three months accelerated studies. Three months satisfactory accelerated data mayB-again, that is subject to CMC review and that is the difference between our application review process and the monograph process, that we deal with every product based on the particular product, the particular manufacturing process and the information provided in the submission. That may allow for up to 24 months expiry.

What about drug product information and

the agency expectation of information in the application? Drug product is a marketed dosage form designed to consistently deliver the drug substance at the desired rate; obviously at the desired site as well.

Complexity of the drug product can arise from different factors such as physicochemical, thermal stability of the formulation components, the route of administration, the onset of action, the site of action, dosage form and drug delivery system. I thought about providing some more specific, concrete examples in each case but that slide would have been as complex as our map that you saw at the beginning of this workshop.

We would like to see a description and composition of the formulation of the drug product; a list of all components used in the manufacture, even the ones that could be removed during manufacturing such as solvents. This is very important.

For composition of the drug product we would like to see a quantitative composition of the

drug product, a list of sub-formulations. We would need to see the colors and the flavors that are used and the list of excipients. It is important to notice, however, when it comes to excipients that excipients are on the active list for the same amounts and dosage form used you do not need to qualify these excipients. So, if you use some of the excipients where we have a clear understanding of their potential safety, etc., then there will be less of a requirement as far as a need to qualify those excipients. If you use others that are not on the list, or different amounts, or in a different dosage form you need to provide such information.

To continue on with drug product expectations, as with drug substance, we need to know the name and the address and the contact information of the manufacturer. We need to have a description of the manufacturing and packaging process, including process controls and the container closure system. For sterile drug products we will need sterility assurance of these

products. I am referring you here to a guidance, CGMP guidance for aseptic processing for sterile drug products. You will find the information there fairly useful.

Drug delivery system if appropriate. I think if you use the most simple oral solids available there is less of a need to provide additional information but for some of the modified release dosage forms, some of the transdermal patches for example or inhalation drug products we will need to see some of the information you have in the development in order to ensure the quality of these products.

Environmental assessment requirements and expectations are listed on the slide, and there may be situations I think in many of the cases that you may have where a waiver could be used where you don't have to provide detailed environmental assessment information.

Shelf life and stability. We establish shelf life based on appropriate stability data and testing protocol and relevant information,

stability protocol and storage conditions. We talked about the accelerated and room conditions earlier. They are the same as for drug substance. Test and acceptance of criteria; testing frequency; submission expectations. For NDAs it is three batches. I missed a "B" here; it is ICH Q1A and B.

What about specifications? Specifications are the quality standards that are intended to assure safety and efficacy. When we talk about specifications using ICH language, if you wish, we are referring to the test, the analytical procedure and the acceptance criteria. I think most commonly we will use that acceptance criteria as the specification while detaching it from the attribute itself and the analytical procedure used. So, it is fairly important, and we expect both for new drugs and generic drugs, that you will use these three components of the specification when you share your information with us. Examples of some of the specifications that we expect to see and to evaluate in order to ensure safety and efficacy are

things as simple as appearance, assay potency, in-vitro dissolution or disintegration, impurity profile, content uniformity, and other critical quality attributes as appropriate. For example, if you are using an oral inhalation product there may be some additional attributes that you need to evaluate in order to assure the appropriate delivery and, hence, the safety and efficacy for that particular product.

USP monographs and public standards are considered as minimum requirements. So, if there is a USP monograph you may have to meet these expectations. However additional specifications may be needed. That clarity could be provided when you meet with us and when we look at the specifics and particulars about your drug product.

Some additional considerationsB-all facilities used in the manufacture of the drug, that is, drug substance, drug product, packagers, testers, etc., should be ready for inspection upon submission of the application. So, when you submit the application to us, the places where you will do

the testing and manufacturing and packaging have to be prepared and ready for our pre-approval inspection.

Facilities should operate under current CGMPs and here is the citation of the regulation, both 210 and 211, and the website. Inspection will evaluate conformance to CGMPs and to the information in the application as well.

I would like to thank you for your attention. Feel free to call our office. Here is the phone number. Better yet, you can call Michael Folkendt who is our supervisor department manager. Michael can be reached at 796-1670. We are currently located in White Oak and here is his email address. With that, I thank you for your attention.

MS. AUTOR: We are now ready for a break. We are going to start promptly at 10:15. You will notice cards around. They are at the registration table. They are in both overflow rooms, 102 and 204. We are going to be collecting questions. Please print your questions legibly. We will

present your questions at the Q&A. We will be coming around and collecting them and passing out more cards. Thank you.

[Brief recess]

MS. AUTOR: We have a pretty ambitious agenda today so we would like to get started again. Our next speaker will be Mr. Gary Buehler, who is the Director of the Office of Generic Drugs. Mr. Buehler is a pharmacist and he was appointed as director of OGD in July of 2001 after serving as the deputy director of that office since 1999. Mr. Buehler has worked for FDA since 1986. Prior to joining the Office of Generic Drugs he was a senior regulatory project manager in the Division of Cardiorenal Drug Products and, as I said, he has been running the Office of Generic Drugs which, as we know, is a very busy, very important place, since July of 2001. Thank you, Gary.

**Regulatory Pathway: ANDA**

MR. BUEHLER: Thanks, Deb. I hope everybody is back by now. I usually begin most of my talks with a propaganda statement about generic

drugs. They are used in over 50 percent of the prescriptions filled today. Actually, if you count the number of units it is over 60 percent of the units dispensed that are generic drugs. They save the American public millions and millions of dollars. But since I don't have time today to do that, I will get right into my talk.

[Laughter]

The purpose here is to talk about the ANDA pathway for unapproved drug products. It is a fairly limited pathway. If you look at the little guide that Michael provided and that Dr. von Eschenbach commented on, we are in the upper left-hand corner and we actually just occupy a couple of boxes. Why is that so? The requirements for generic drugs are that they have to have the same active ingredient or ingredients, the same route of administration, the same dosage form, strength, and conditions of use compared to the reference listed drug or the brand name product. Every generic product must have a reference listed drug to compare to because when we approve generic

products we rely on the findings of safety and efficacy for the particular reference drug in the approval process for generics. So, that is a very key point in the presentation today. In order to submit an ANDA, there must be a reference listed drug, except for an exception that I will go into.

Now, how do you find the listed drugs? You find the listed drugs in FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations," or what we call the "Orange Book." And, I have brought one. One of the judges in one of our lawsuits actually asked if it was orange--

[Laughter]

-Band, in fact, you can see it is orange. At least the people in this room can see that it is orange. We used to sell these for $101. I am not quite sure how we arrived at that price, $101, but it sort of, you know, complies with the FDA way of doing thingsB-not easy! It also gives an idea of the FDA's business acumen because we used to get actually $101 for each one of these and the

supplements and then we decided to put it on the website for free! Amazingly so, the sales dropped off dramatically!

[Laughter]

So, you can no longer get one of these. This is actually the last "Orange Book" that was published. It is the 2004 edition. You can't get an "Orange Book" now but, as I said, you can access it for free on the website. Also, it is a good thing because right now the "Orange Book" staff is contained in the Office of Generic Drugs. We actually control all the entries into the "Orange Book" and we make daily entries into the "Orange Book" when an abbreviated new drug application is approved, especially for a first generic because many pharmacies in this country will not substitute a generic drug unless it appears in the electronic "Orange Book." We found that even though there was a five- or ten-day lag in putting these entries into the "Orange Book" some pharmacies refused to fill the product with the generic unless it was in there. So, we actually have done daily listings so

this becomes outdated within a couple of days. So, it is just as well you can't buy it anyhow.

This is what it looks like, the cover. The "Orange Book" contains the therapeutic equivalence codes for all NDAs, OTCs and ANDAs. Anything that has an "A" preface is a substitutable product. Anything that has a "B" preface is an inequivalent or non-substitutable product. We no longer approve B-rated products. B-rated products are sort of holdovers from the past. They are safe and effective products that have been approved by FDA; they just are not equivalent to any particular reference product.

Reference listed drugs and brand names are identified by FDA for generic companies to compare their proposed product. A reference listed drug in the "Orange Book" is denoted by a little + next to the particular entry.

This is what the electronic "Orange Book" looks like. It allows you to search electronically a number of fields, either the trade name, brand name, whatever, so that you can find what you are

looking for there.

Now, this is the one exception to not needing a reference listed drug, and that is a suitability petition. An ANDA for a product is not identical to the listed drug in route of administration, dosage form, strength, one active ingredient in a combination with another active. These are what you can put a suitability petition in to us for. What a suitability petition does is it is your request to us to put in an ANDA for a product that does not have a reference listed drug. You are using one of these options as the exception. In other words, if there is a reference listed drug with one particular route of administration and you want to pursue another route of administration you could put in a suitability petition in for that. The same for dosage forms. A common suitability petition would be a tablet for a capsule. The reference listed drug is a tablet and you want to put in a capsule form for that particular product. Strength, if there is a 50 mg and 100 mg of the reference listed drug and you

want to put in a 75 mg to allow people to titrate easier. Or, one active ingredient in combination for another with an active. The combination here is Percocet and you want to put in acetaminophen for aspirin or the other way around. For a combination, usually they are analgesic combinations where you want to submit one component for the other.

Now, I have listed PREA on this slide at the end and Dr. Mathis is going to give you a nice presentation on pediatrics this afternoon, and she is going to go over PREA. But I do want to say that PREA has affected the way we evaluate suitability petitions because when you are changing anything but the strength PREA can affect whether we will approve your suitability petition or not. PREA is Pediatric Research Equity Act and, again, Dr. Mathis will go over that and make you very knowledgeable on that this afternoon. Thank you, Dr. Mathis.

505(b)(2) NDAs is another potential option. 505(b)(2)s are, you know, variations of

either ANDAs or NDAs and Kim Colangelo will go over 505(b)(2) options this afternoon and I thank her for that too.

Let's go over patent certifications. If you put in an ANDA your ANDA must contain a patent certification. The Act requires that it contains a certification to each patent listed in the "Orange Book." Only patents listed in the "Orange Book" need to be certified. Now, some drug products may have other patents that do not have to be listed in the "Orange Book." This doesn't absolve you from complying with the patent or getting sued over that particular patent. It just means that you don't have to put a certification into the Office of Generic Drugs for that particular patent.

Paragraph I certification means that patent information relating to the innovator drug has not been filed. Paragraph II means that the patent has expired. Paragraph III means that you don't expect your ANDA to be approved until the particular patent will expire. Paragraph IV is the one you hear most about. This is a patent

certification where you are challenging a particular patent that is listed in the "Orange Book."

Now, a certification under paragraph I or II means that your ANDA can be approved when it is immediately otherwise eligible. In other words, when you fulfill all the scientific and regulatory requirements in your application your ANDA can be approved. For paragraph III, again, you are waiting until the patent will expire.

For a paragraph IV certification, where you are challenging a particular patent, there are a number of requirements you have when you put in that paragraph IV certification. When you file a paragraph IV certification to a listed patent you must notify the patent owner and the NDA holder for the listed drug that you filed an ANDA containing this patent challenge. If either party files a patent infringement suit against the ANDA applicant within 45 days, then your application will have a 30-month stay of approval to allow the patent litigation to go forward.

The statute provides for an incentive of 180 days of market exclusivity to the first generic applicant who challenges a listed patent by filing a paragraph IV certification. So, this is the incentive for filing a challenge to a listed patent in the "Orange Book" that you can get 180 days of market exclusivity.

Now, in comparing the NDA to the ANDA review process, it is really quite similar and I do thank Moheb for going over in detail the CMC requirements. They are very similar to ANDA and I will not repeat what Moheb said today. Chemistry, manufacturing and controls are very analogous. Labeling has to be the same as the listed drug with certain exceptions. The testing, the inspections and such are the same as what was done for the NDA process. The differences for an NDA versus an ANDA lie in the animal studies, clinical studies and bioavailability requirements for an NDA. In lieu of that, we have our bioequivalence study in the ANDA.

This is a very busy slide and I really

don't want to go through it in detail, but it does provide to you a schematic of the ANDA review process. A couple of things, up at the very top, we do a very thorough filing review in the Office of Generic Drugs. Part of the reason for that is to make sure that the applications submitted to us, and especially applications with paragraph IV challenges, are complete applications. There is tremendous competition to get your application in when you are challenging a patent and to be first. Obviously, there is a very large reward for being first to challenge a patent. So, we are very vigilant in the Office of Generic Drugs when we file these applications to make sure that the study is credible; that the bioequivalence study in the particular application is a credible study and that all the other requirements of the ANDA are fulfilled. So, we have a very in-depth filing review and our filing template is on our website, which I provided at the end of my talk, and you can pull up the filing template to see what our filing people do look at.

Once it is filed it goes into our review areas. Also, at the filing stage we request the particular inspections required for the ANDAs. We do this at the filing stage because, in case anyone hasn't heard, we have a fairly large backlog of applications in the Office of Generic Drugs. So, in order to not allow the process to wait we want to get the requests for inspections into the Office of Compliance as soon as we can. That is why it is done at the filing stage so that the request can actually be queued up in the Office of Compliance and we are not held up by inspections at a later period.

We do have review queues. We have review queues for each review discipline. Chemistry, bioequivalence, labeling and microbiology all have separate review queues. These disciplines review particular portions independently. Once everything is all okay we, hopefully, will give you your approval.

Now, as I said, the labeling has to be the same as the brand name labeling. You may delete

portions of the labeling protected by patent or exclusivity. One of the little blocks in the flowchart actually says that you have to have the same conditions of use I think, or labeling, and you can delete certain indications of your labeling that are protected by exclusivity as long as there are some indications that are not protected that you can market your product on. Your product may differ in excipients, PK data and your "how supplied" section. You don't have to market the same sizes as the RLD or the same number of sizes.

This is a very, very brief rundown of what we look at for chemistry: components and composition; manufacturing and controls; batch formulations and records; description of facilities; specifications and tests; packaging; and stability. Again, Moheb has given a wonderful overview of this in much greater depth.

I did want to provide one slide that would give you the differences in the review of an ANDA versus an NDA. Again, Moheb also went over this too. We require three months of accelerated

stability to be submitted with the application. So, you have to have three months when you come in the door and the filing people will look at and assure that those three months are in your application. We also ask for available room temperature stability data, and we will ask for an update when we get closer to approval. You are to generate, of course, room temperature stability data while your application is under review at the Office of Generic Drugs. At some point, when we are close to approval we will ask for your available room temperature data to make sure that the stability is holding up. As Moheb said, if your three-month accelerated stability does not show any degradation and your room temperature stability that you sent to us is acceptable, you will probably get a 24-month expiry for your product.

Now, you have to make one demonstration batch. This demonstration batch will be the source of your bioequivalence study product so that the product you use in your bioequivalence study should

be from this batch. It will also be the source of your stability and dissolution data that you will submit to us. And, you must submit a complete batch record for this batch and we will review that batch record.

I want to get into the bioequivalence study and go into a little detail on just how we evaluate bioequivalence in the Office of Generic Drugs. The definition is, you know, rather formal. It is pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions. What does this mean? It means that you have to do a study and compare your drug to the reference product. And, you have to do it, for the most part, for standard oral products in human subjects.

Now, the purpose of bioequivalence is that pharmaceutical equivalence, which we will determine through our CMC review, plus bioequivalence will equal therapeutic equivalence to us.

Therapeutically equivalent products can be substituted for each other without any adjustment in dose or additional therapeutic monitoring. The most efficient method of determining therapeutic equivalence is to assure that the formulations perform in an equivalent manner.

This is just a schematic of oral dosage form performance. As you can see, there are a number of places where we can evaluate oral dosage form performance. We can look at how the product dissolves, the dissolution of the product. We do use dissolution in a number of ways, most notably in evaluating the stability of your product. Usually stability protocols depend upon the dissolution of a particular product at certain time points, and we can see if the dissolution degrades, changes or whatever, that something is happening in that particular dosage form. Also, further down as you swallow the dosage form and get into the GI track, you can have the measurement of how the active ingredient is absorbed from the bloodstream. That is the pharmacokinetic measurement. Then, if

you go all the way down, you can actually look at the clinical or pharmacodynamic measurement to make a determination of how the product exerts its clinical effect.

A lot of people come to us and we get criticism because we don't compare the pharmacodynamic effects of generic drugs to the reference listed products. We actually get citizen petitions submitted to us saying, you know, our drug is very unique and we think the only way that you can make this comparison is to compare it in the clinic and do a clinical trial setting of our drug compared to the generic drug.

Well, we don't really agree with those characterizations and this is why. Basically, if you are comparing a pharmacodynamic response and you have the wrong dose, if you happen to have the dose up here you are not going to get any difference no matter if there is a difference in the absorption of the products or not. You know, as we know, there is a certain point at which drugs exert an effect and they stop exerting an effect

and they plateau and they get up here in their pharmacodynamic response. So, to try to compare generics and try to think that we can hit this point where there is actually a dose response and be able to compare the generic to the reference product and get some kind of a precise measurement, we believe, is very unlikely. So, that is why we only use a pharmacodynamic measurement when we have to; when we can't use a pharmacokinetic measurement.

Now, using PK we have the dose of the drug down here and the plasma concentration on this axis. So, the more dose we give, the higher the plasma concentration is that we get. This is assuming a drug with linear kinetics. So, we can make a very precise, very nice comparison between the reference listed product and the test product or the proposed generic product.

How do we do this? Well, the two standard designs are single-dose, two-way crossover, fasted and a single-dose, two-way crossover, fed. So, how do we go about doing this? Well, we round up about

two or three dozen folks. Let's say we maybe look at the first three rows here and we get them in a room and we would first determine that we have a diverse population. We need a couple of young folks and a couple of old folks and we need some women in there too. That would be good so that we would have a good representation of the population of America, the "Melting Pot." That is a recommendation, to have a diverse population.

We would give each of these individuals the test drug and measure the amount absorbed at certain time points, depending upon the half-life of the drug. If it is a very short half-life we would start measuring the time points very quickly and they would be very closely spaced. If it is a long half-life drug it would be strung out a little bit further. Then, at a certain point when that drug is washed out of their system we would give them the test drug so that we would measure the test against the reference, using the individual patients as their own controls. So, we are basically using the comparison in each individual.

Now, sometimes we can't do this. If we have a particularly long half-life product like amiodarone or etidronate we would need to do a single-dose, parallel, fasted study where we would do single dose in a group of people, you know, in parallel groups of people and compare that test to reference.

Sometimes we have to do a replicate design which means we just repeat the process over again, test-reference, test reference, because with highly variable drugs you will get a lot of variation and you want to try and smooth out the variation with more time points. Sometimes we do multiple-dose, two-way crossover, fasted and these are less sensitive and usually this is when we cannot do normal subjects in our studies, such as clozapine and chemotherapy trials.

Finally, we have to do clinical endpoint trials when we have products that are not absorbed in a significant enough fashion so that we can measure the active ingredients. We do these primarily for topical products where, if you want

to get an antifungal approved in the Office of Generic Drugs, you would have to roundup around 500 people with athlete's foot and divide them into two groups and give half the test and half the reference and compare the pharmacodynamic response in these two groups. They have to meet within our particular 80-125 parameters to be approved. It is a very onerous study and we are working very hard and doing research to try to find surrogate methods to do this type of a study so that you don't have to do this kind of a study for topical products.

We do have waivers for in vivo bioequivalence studies. If you have a parenteral solution, and the requirements for a parenteral solution are that it has to be Q1/Q2 the same, which means it has to be quantitatively and qualitatively the same as the reference listed product. And, the formulation for the reference listed product is publicly available. So, you can determine what the formulation for the RLD is and, if you come in with a parenteral solution and you are Q1/Q2, you can requestB-you still have to

request it but you can request a waiver of in vivo bioequivalence and we will grant it.

For inhalational anesthetics that are solutions, for topical skin solutions, not suspensions but solutions, for oral solutions, and if you have a different proportional strength of a product for which you have already demonstrated bioequivalence, and that means that if the "Orange Book" denotes that the 25 mg strength of your product is the reference listed drug so that that would be the strength with which you would do your bioequivalence study and there is a 12.5 mg and a 6 mg and a 3 mg, you can actually get a waiver of bioequivalence for the 12.5 and the 6 and the 3 as long as they are proportional in composition to the 25 mg, to the product that you did your bioequivalence study on and that the dissolution is comparable.

Now, I am not a statistician and I am not going to dwell on the statistics of how we figure out whether you are bioequivalent or not, but I will give you the parameters. We use AUC, which is

area under the curve, and Cmax, which is maximum concentration, as our primary variables that we look at for bioequivalence. Your 90 percent confidence interval must fit between 80 and 125, and I will go over some of that.

It is a two one-sided test procedure which shows that test is not significantly less than the reference and reference is not significantly less than test. Our significance difference is 20 percent. We express all data as test over reference so we have 80 over 100 which gives you 80 percent as the bottom. We have 100 over 80 which gives you 125 as the top. People ask us often why do we have 125 at the top instead of 120. This is why. So, our interval that you have to fit between is 80-125.

What does all this mean?

[Laughter]

Can there be a 46 percent difference from the generic and the reference? No, there can't be a 46 percent difference. What do we mean when we talk about your point estimate? And, what is a

confidence interval? And, why are we so persistent about the confidence interval?

Well, these are some possible bioequivalence results. The one at the top, that is the way you want your study to look like. You can see we have an 80 and a 125 boundary. Those are what you have to be between and the little line at the top is where the point estimate is. What the point estimate is, is when you take all of your subjects and you give them the test product, that establishes what one will be. In other words, one between 80 and 125 is right in the middle here. To establish what your actual target point will be is the responses that your subjects get to the reference product. So, you round up all of the results from your subject and you create a curve with these results and the averages of all those results end up to be your point estimate. That is the average and that is your target when you do your comparison with your test product.

So, the confidence interval is a measurement of the variability that you have seen

between the comparison of the reference product to the test product. So, if you have a very wide confidence interval, such as this third one, what it means is that your averages actually fell right in the middle, but the problem is that your product was so variable that it fell outside of both the lower and upper range. So, that would be akin to your product being 100 percent bioavailable but you had a lot of people absorbing it at a 60 or 70 percent range and a lot of other people absorbing it at a 110 or 120 percent range. So, it is not a great product. Yes, you somehow lucked out and, you know, your average is in the middle but it is not a product that we would want to put on the market because of the variability of the comparison between yours and the reference product. So, it is not a substitutable product.

For this product, on the other hand, the point estimate was right about in the middle with an equal distribution going both over and under and well within the confidence intervals that would be our acceptance criterion.

This product is an approvable product. It has very low variability because the confidence interval is so small, so tight. You know, its absorption is a little bit off from the point estimate but it is a predictable product and it is not highly variable so that product would be absorbed.

These products are just downright bad and, you know, they wouldn't make it at all. Another thing I want to mention is that the Office of Generics is not like horseshoes. You have to be within these confidence limits. If you go outside by, you know, just a couple of percentage points or tenths of percentage points you will fail. You will not be approved. I just want to make that clear. Don't come in and say, gee whiz, we are really pretty close. That is really nice but you still fail. That is why you have to make sure you have enough people in your studies so that you will have enough power to get the results you want to. We leave that up to you and your statisticians. You can have as many people in your study as you

want. We do recommend that you don't have less than about two dozen.

Now, for resources, we don't meet with people individually in the Office of Generic Drugs for pre-meeting submissions. We had over 800 submissions last year. We absolutely do not have the manpower to meet with everyone individually so we do ask you to look at the regulations, the guidances. The Generic Pharmaceutical Association has a lot of information. Our website has a lot of information, which I have provided to you. So, we do welcome your applications. Please, put them in line with the rest of them. We will do them as quickly as possible. And, it has been my pleasure to be here and give you this information.

MS. AUTOR: Thank you, Gary. Our next speaker is Kim Colangelo. Kim is the Associate Director of Regulatory Affairs in CDER's Office of New Drugs. She is responsible for providing guidance on regulatory and scientific policy and administrative matters in the Office of New Drugs and serves as the leader for two teams of project

managers, providing regulatory support for many initiatives within OND and the Center. It is a very big job and she has been with FDA since 1996.

**Regulatory Pathway: NDA Process**

MS. COLANGELO: Good morning, everybody. It is my pleasure to be here today to talk to you about the pathways available to you should your product not qualify for either the OTC monograph or the ANDA process. I am going to tell you everything that you need to know about an NDA in the next 20 minutes so buckle your seatbelts.

Actually, what I am going to be doing is providing you an introduction to the process, a high level look at the information needed to be submitted within an NDA. I am going to be talking mainly about the format and about some of the regulatory requirements, but I am going to happily defer information specifics about the technical requirements to the speakers who will be speaking to you this afternoon, as well as Dr. Nasr who covered chemistry this morning. You will find in the course of my talk that there will be references

throughout to websites where a lot of additional information can be found.

Like any good, self-respecting government agency, the first thing we require you to do to submit an NDA is to submit a form. Form 356h can be found at the website located here and looks something like this.

Basically, this form is meant to provide just some basic information about your application, the product that you are submitting, the indication you are proposing and, more importantly at least for us, the name and the contact information for the person who will be responsible as your regulatory contact. In addition, there is a list of items that are required to be submitted in the NDA. I think you will find this very helpful on the back of the form, kind of a checklist for you to make sure you have all of the information needed.

So, looking at that checklist, the next thing we need is an index or a table of contents. If you think about the amount of information that

needs to be compiled to provide us with enough information to determine that your product is safe and effective to be approved and marketed to the American public, there is a lot of information that is going to be provided to us and our review staff needs to have an index and table of contents, whether paper or electronic, in order to navigate your application and to find the information that they need.

Following that, we do have a summary section. Of particular note to you, this would be the area where you would want to provide any marketing history relevant to your product. In addition, this section will contain your proposed package labeling and a summary of each of the technical sections of the NDA. The technical sections will include all of the information relevant to support the approval of your product, the clinical information, chemistry information, nonclinical pharmacology and toxicology, human PK and the statistical information.

In addition, we ask for information

regarding pediatrics, patent information, and financial information such as financial disclosure. Financial disclosures are required for all investigators who conduct trials on behalf of you to support the approval of your application. All of this information can be found in the Code of Federal Regulations summarized in 21 CFR 314.50.

There are a couple of different ways to submit an NDA. Acceptable formats can be what we refer to as the traditional format, and that would follow the outline which is on the back of that form, the 356h or that is encompassed in 314.50 of the CFR. In addition, the common technical document, or CTD as it is sometimes referred to, is more of an international format for submitting. Again, the information in these application formats will be the same but the organization of the information will be slightly different. What the CTD format allows you to do is to submit the same application to the U.S. as well as the European Union member countries and Japan. Your application can also be submitted in paper format, although I

will point out that all of your product labeling must be submitted in electronic format. Your application can be submitted entirely in electronic format if you so choose. Or, for the traditional application format only you can submit a mixture of both electronic and paper documentation.

There is a link to a website that I think many of you will find helpful that has a lot more detailed information about these formats and a lot of additional general information. It is a small business website that CDER provides.

One thing I wanted to point out, a recent change as of June 30 of last year, is that all new applications for prescription drugs or over-the-counter drugs, as Dr. Tan talked about earlier today, have to follow the drug facts labeling format but prescription drug format labeling has a whole new look. This new format is now required for all new applications. It is referred to as the physician labeling rule, or PLR. The look of the label has been changed dramatically to make it a lot more user-friendly

and more informative for the healthcare provider and prescriber.

You will find that the front page looks similar to this and is comprised of a section that contains highlights, important prescribing information or will contain information about how the product is supplied; what the active ingredient is; what the approved indications are; any recent labeling changes and, of course, any important safety information. All of that is contained in the top section, referred to as the highlights.

The bottom half of the first page is a table of contents. This will actually allow prescribers to get to a section of the label a lot easier to find the specific information that they are looking for.

The website that I have listed here will provide you not only with valuable information such as frequently asked questions and guidance documents related to the implementation of this rule, but also provide you with examples of products using this format.

One of the things you have heard a lot about this morning is reference to what we call 505(b)(2) applications. So, what I want to do now is talk a little bit about what the difference is between what we refer to as a 505(b)(1) and a 505(b)(2). When we talk about section 505(b) what we are referring to is the Federal Food, Drug and Cosmetic Act. All new drug applications are approved under section 505(b) of the Act. It is important to note that the standard for approval, substantial evidence of safety and effectiveness, is the same regardless of whether you are submitting a (b)(1) or a (b)(2) application.

However, what is different is the source of the data. A (b)(1) application is an application for which you either have right of reference to the data or the data is owned by you. It could be conducted by a contract organization but you purchased the information or it could be studies that you have done in your own right.

The focus of today's meeting, however is that, I believe, most applications that we will be

talking about really are going to fall under (b)(2). This is an application which relies upon information which you do not own or have right of reference to, including published literature.

505(b)(2) applications are often submitted as changes to already approved products. Some of the changes that are acceptable as a 505(b)(2) NDA, you will see that some of them are the same as what Gary just spoke about with respect to OTC or generic products with suitability petitions. These products can also be submitted as 505(b)(2) for changes in dosage in dosage form; formulation; strength; route of administration; dosing regimen; indication; and active ingredients, such as a different salt. It is important to note that if you have a different salt than one that is already marketed cannot be submitted as a generic product but must come in through the (b)(2) route. In addition, substitution of an active ingredient in a combination product, or a combination of two previously approved products. Monograph deviations are also submitted under a 505(b)(2), as Dr. Tan

talked about this morning, as well as the DESI products.

There are two links here for information. One is the draft guidance for industry for applications covered by section 505(b)(2). But one of the more recent documents is a response to a citizen petition. Actually, it is not one, not two but three citizen petitions, which were received by the agency, which actually challenged our authority to approve products under 505(b)(2). I think if you are interested in getting additional regulatory history and background about the (b)(2) process or have a desire to know what types of products we have already approved under the (b)(2) process, you will find this a very interesting read. If not, and you are having trouble sleeping I highly recommend this document!

[Laughter]

So, what is so special about a 505(b)(2)? As I said before, you can use this pathway to rely on general information such as non-product specific published literature, or you can specifically rely

upon our previous finding of safety and effectiveness for a previously approved product. If you choose to rely on something that we have already approved you have to submit a scientific bridge to the approved product. Generally this is done by submitting bioequivalence or bioavailability data. It also requires patent certifications and statements.

I am very pleased that Mr. Buehler has already covered patent certifications in detail so that I don't have to, but (b)(2) applications do follow the same rules for patent certification as generic drugs. You have to submit, to the best of your knowledge, patent certifications for any patent listed in the "Orange Book" and, at this point, Gary, if you could hold up the "Orange Book" again-there is my visual aid, right there. You have to certify any patent listed in the "Orange Book" for a product that you are referencing to provide support for your application. The types of patent certifications that Gary already covered are contained in 21 CFR 314.50.

Now that you know everything you need to know about all of the information that needs to be contained in your NDA, I am going to tell you what we do with it when we receive it. The first thing that happens when your NDA comes in the door is that it is looked at by a regulatory project manager. Our regulatory project management staff have scientific degrees, scientific backgrounds. They are considered the regulatory experts for the process. They manage the application review and they will become your best friend so treat them well. They take a quick look at the application to make sure that it is complete; that we have the information that we need; that all of those checkboxes on the back of the form 365h have information in them; and that we can then distribute them to our technical review staff, our clinical reviewers, our chemistry reviewers, our pharm/tox reviewers, etc.

The first thing that a review staff does, besides groan heavily, is they take a look at the application and they do a filing review. What a

filing review is, it is a review that is more quantitative than qualitative. It is an effort by the review staff to make sure that they have all of the information that they need to make a determination on whether or not the product can be approved. This type of review is required to be completed by day 60 after we receive your NDA.

After they determine that your application is filable they will begin the actual in-depth review of the data that has been submitted. While the reviews are done independently, there is a tremendous amount of interaction between the members of our review team to communicate about findings and data that they have reviewed, to keep each other apprised, and to get input and guidance where needed from cross-discipline information.

Once the technical reviewer has completed their review they pass the review off to what we call a secondary reviewer, or a team leader. This is a senior member of our review staff who takes a second look at the data and provides a second level of determination on the appropriateness of the data

to support marketing.

Finally, all of these reviews are fed down to the signatory authority, in most cases the division director and in some cases this is our office directors. They will take a look and it is their decision ultimately to determine whether or not the application can be approved, is found to be approvable or not approvable. This determination will be done within six or ten months, depending. Six-month reviews are done for priority review products. Those would be those that provide a significant public health benefit or for serious and life-threatening illnesses.

So, let me give you a little bit of advice before I wrap up this morning. The first thing you need to do is you need to research available guidance documents. There is a lot of information that is available and is out there that will be helpful for you as you proceed down this pathway. Do a thorough literature search for information regarding the active ingredient in your product. And, we do actually offer meetings with individual

companies to talk about their proposed application so we suggest that you actually request such a meeting with the review divisions. If you do not know which review division in the Office of New Drugs will be responsible for reviewing your application, I direct you to that website. You will find that the Office of new Drugs is comprised of 17 review divisions, primarily organized by therapeutic area. So, if your product is an antihypertensive you will be contacting the Division of Cardiorenal Drug Products.

The person that you will want to be contacting within the division to start this process will be the supervisory regulatory project manager. If you don't know how to request a meeting, there is a guidance document available, formal meetings with sponsors and applicants for PDUFA products, which outlines all of the requirements for requesting a meeting; the information that is required to hold a meeting. It gives you an overview of the timeline. It tells you what to expect with regard to the agency's

response.

Now, I don't want you to be misled. The PDUFA products does cover everything. It does not matter whether or not you will be subject to a user fee or not, and I am happily going to leave all questions regarding user fees to Mike Jones for this afternoon. But this process does cover all products which will be submitted as NDAs.

I thank you for your attention. I know we will be taking questions later on in the morning.

MS. AUTOR: Thank you, Kim. Our next speaker will be talking about demonstrating product effectiveness for NDAs, and that is Bob Temple who is the Director of the Office of Medical Policy, as well as the Acting Director of the Office of Drug Evaluation I. The Office of Medical Policy is responsible for assessing quality of clinical trials and for regulation of industry materials through the Division of Drug Marketing, Advertising and Communication, DDMAC. ODE I is responsible for the regulation of cardiorenal, neuropharmacologic and psychopharmacologic products. Dr. Temple has

been with FDA for a mere 34 years and spent about a decade as final sign-off for CDER on DESI drugs. He has a long interest in design of clinical trials and assessment of evidence, and is the best expert we could have to talk about this subject.

**NDA/Demonstrating Product Effectiveness**

DR. TEMPLE: Good morning. I probably have more slides about effectiveness than you really want to know and I will try to rush through some parts. Anyway, let me begin. I am going to talk about the more difficult cases that Deb showed in the beginning. If the drug is DESI effective you are probably not going to have to do new trials. If it has an approved new drug application and is ANDA eligible or some variance is allowed, you are probably not going to have to do trials. There might even be situations where the drug is part of a combination and there is really good data on what its effectiveness is and there too it may not be necessary to do trials. Those are going to be mostly about biochemistry, bioavailability, things like that.

If the dosage form is different there may need to be a study. Sometimes you can get a suitability petition for those, almost always if it is just a tablet/capsule switch. If it a controlled-release product sometimes you need trials, sometimes you don't. And, almost always if there is a change in route for a known material you will need some kind of studies. So, what I am going to talk about is going to be relevant to those situations where a study is needed.

If the effectiveness of the active moiety is not established approval requires that it be established. Generally the route for doing this is the new drug application and I am going to talk about the effectiveness standard that applies to new drugs. The effectiveness standard for inclusion of an OTC product in a monograph isn't all that different. In fact, for practical purposes it is pretty much the same.

The hope of establishing that something is generally recognized as effective is in all

likelihood an illusion. I wouldn't want to say it couldn't be done but it is very hard. The standard for recognition of something as generally recognized as effective was set by the Supreme Court in Hynson, Westcott and Dunning and it requires a consensus among experts based on literature of the same quality and quantity needed to approve a drug under section 505. It is not an escape clause, just to get that out of the way.

The legal standard for effectiveness was described in 1962 in section 505(d)(5) of the Food Drug and Cosmetic Act. It was slightly modified by FDAMA in 1997. Substantial evidence is the standard for approval. There needs to be substantial evidence that the drug will have the effect it is represented to have in labeling under the conditions of use that are prescribed. The substantial evidence requirement alone wouldn't be a particularly high standard. It is not as high as beyond a reasonable doubt, the criminal standard. It is not even as high as "preponderance." Somebody, -maybe Peter Hutt but I

am not sure described substantial evidence as something between a scintilla and a preponderance.

[Laughter]

However, the people who wrote the 1962 amendments made an intelligent compromise. They said the only way to demonstrate the required substantial evidence was through adequate and well-controlled investigations that demonstrate the drug's effect. So, substantial evidence is not an especially high standard, but the way you have to show it makes it a high standard. Not only does there need to adequate and well-controlled investigations, but people looking at those results, qualified experts, must be able to fairly and responsibly conclude that the drug will have the effect represented in labeling. So, the studies have to be well designed and they have to show something. What they have to show is what is described there.

It has been established in Warner-Lambert v Heckler that the experts we are talking about here who will have to reach that conclusion that

the drug has an effect are FDA people, and the effect has to be not just anything the labeling says but it has to be meaningful. There was once a DESI drug that increased bile flow. Nobody could ever figure out why that was a useful thing to do. That would not be a suitable claim until you knew that it had some meaningful effect.

The plural in investigations ("adequate and well-controlled investigations")was intended by the people who wrote it. They said so. But FDAMA, in 1997, allowed reliance on a single study plus "confirmatory evidence." What that means has never been entirely clear but it is fair to say that for drugs that are intended to provide symptomatic improvements it would be unusual for us to accept a single study. I will talk about that a little bit more.

It is worth remembering that this is not a statement that you need two identical studies. In fact, usually we don't particularly want two identical studies. It is better to have studies of different doses, maybe even slightly different

populations. And, we have a guidance describing how we weigh evidence of different kinds in reaching a conclusion. It is called Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, made available in 1998 in response to FDAMA. It is on our website. So, the legal standard is twofold. The supportive studies need to be well-controlled and they need to be convincing. I am going to spend a little more time on what well-controlled means. What convincing means as a historical matter is that these well-controlled studies, properly analyzed, show what has come to be described as statistical significance, which usually means a two-sided p value of less than 0.05. Anybody could spend a lot of time pointing out that that is arbitrary and can't be proved but it would be a disaster to have to figure out what the significance level was in every study. Sometimes people would say it should be 0.001 if they really don't like the drug, or sometimes they would say it should be 0.1 if it is a bad disease with no treatment. Using P less than

0.05 avoids that discussion although there is, in fact, some degree of flexibility. We have over the years, even before FDAMA, sometimes relied on a single very strong study because it was obvious that it was reasonable to do that.

Our regulations at 314.126 describe the characteristics of an adequate and well-controlled study. They do it in some detail. I am going to do it more briefly. The first requirement is that there be a comparison of the treatment with some control. Why do you need a control? The answer is because the course of most diseases, most symptoms in most diseases, is variable and if you didn't have a control and you saw a change you wouldn't know whether the drug did it, the person just improved spontaneously, the observer was biased, the patient had good expectations-you wouldn't be able to tell why the person changed. So, you need a control group. Basically, that is a group of people who are just like the people you are testing the drug on except that they don't get the drug. This allows you to distinguish the effect of the

drug from all those other things.

Our rules describe five different kinds of controls. Although when the rule was first put out they were presented in a hierarchical form, there is no hierarchy anymore. That is, they all could be used in appropriate circumstances, but the reality is that some of them are more persuasive than others in particular settings.

The five kinds of controls are placebo, no treatment, dose response, active control, and historical control. A placebo control actually is a no treatment study that is blinded. In an active control trial, a drug is compared with another drug. Those can either be designed to show that the test drug is better than the other drug, a superiority study, or they can sometimes be designed to show that the test drug is not so much worse that you are convinced the new drug doesn't work at all. That is called a non-inferiority study and I will spend a little more time on that. A historical control is used in a situation where the characteristic course of the disease is so well

defined that you can use your expectation of what would have happened and compare that to what happened on the drug. So, when you cure leukemia you use a historical control because you know leukemias don't go away by themselves.

The reality is that for symptomatic conditions, which is probably what most of the drugs we are talking about treat, randomization and blinding are almost always going to be necessary and a non-inferiority or historically controlled trial is unlikely to be persuasive. So, you are probably talking about placebo-controlled trials in most cases or perhaps a dose-response study but these usually have a placebo group as well as several dose groups.

The second major task of an adequate and well-controlled study is minimization of bias that is, elimination of anything that tilts toward one group. A difference present at baseline, for example could make one group likely to do better at the end. A difference in how the test and control drug groups are either chosen, treated, observed or

analyzed can allow bias. That is, if you knew which patient was going into which group, you could put the better patients in one group and the sicker in the other. Or, again if you knew who was in each group, interpret their outcome you could treat one group differently, more favorably, either deliberately or inadvertantly. Or, you can start looking at the statistical analyses and pick out the analysis that works best out of many choices. Anyway, these are the main places that bias can enter a trial and an adequate and well-controlled study is designed to minimize those possibilities.

The remedies are for the most part straightforward. Blinding takes care of patient and observer bias. If you don't know who is getting the drug you can't have any of these biases operative. Randomization makes it reasonably sure that the patients in each group are going to be similar to those in the other group. And, you specify very carefully and we have learned a lot about this over the years and gotten better at it all the procedures and analyses that are going to

be carried out. That avoids such things as choosing the most favorable analysis out of many after the study is done, which used to be common actually, or just having so many different analyses that one of them is favorable by chance. If you study a whole bunch of things one of them is likely to achieve your nominal significance of 0.05. So, all of these possible biases are eliminated in a proper study design.

Then, the last matter is that there has to be enough detail to know how the study was done and what the results are. Nowadays that is hardly an issue. We get detailed protocols. But if you go back into the past--and this is particularly important because one of the things that someone with an older drug might do is look to the old literature, look to studies that were done a long time ago--it is a terrible problem because you can't really read an old study report and figure out what happened. You won't know how patients were picked. You won't know how they were dropped. You won't know how they were analyzed. You won't

know how missing data were dealt with. You just don't know those things, and we discovered that while we were doing DESI. Sometimes you can't even tell how long people were treated.

The basic principles of what a well-controlled study is were described in a 1970 rule, updated in 1985, but I have to say one of the things that has gone on over the years while I have been at FDA and that I have observed with interest is that we have just learned a tremendous amount about how to do studies, things that we had no idea about in the early days. I am going to illustrate a few of them. What I am going to illustrate is the problem of interim looks at data; they need to count all patients; the problem of changing the analyses. I will talk a little about problems of active control non-inferiority trials. A good statistician could explain this perfectly well, but if you monitor results as they come in, that is check for statistical significance as each patient comes in and then stop as soon as you achieve some nominal significance, such as p less than 0.05, you

can show that you greatly increase the chance of having an apparent significant effect even when the drug does not, in fact, work. That is because there is always random variation and if you look at trial results as they come in they will look better; they will look worse; all on a random basis even if the drug doesn't do anything. If you are allowed to keep collecting data and stop whenever you want to it is hard to lose.

So, we now know this. There are many standard ways for allowing interim looks and insisting that before you stop a trial for a good result you have a more extreme result. But we didn't always know that. An example of how we didn't know comes from cimetidine, the first histamine-2 blocker for treatment of ulcer disease. It was approved in 1977. The Sponsor actually did four ulcer healing studies, a 6-week, a 4-week and two weeks. In each, cimetidine was compared with placebo and endoscopic healing was what was looked for.

What they did was monitor the healing

rates continuously. As each case was completed they recalculated the p value. I don't remember whether it said that in the protocol or not, but I don't think people at FDA then even thought about those things at the time. Certainly, we never asked. Anyway, the trials were stopped as soon as the p fell below 0.05. As I said that just gives you a huge inflation of alpha error (the chance of saying a drug works when it doesn’t).Interestingly enough, it didn't really work out for them because while the two short-term studies did show an effect after the four- and six-week studies were stopped, a few more cases came in and the p value went up above 0.05. So, the initial labeling for cimetidine only identified the two-week studies.

But the main point is, as far as I know, no one had ever raised this issue of monitoring interim results before. It had never come up until we saw this and then finally started to worry about it. No one would do such analyses now. But if one were looking at old data in publications from the '60s you would have no idea whether that was done.

Anyway, now if you want to do interim looks we have methods. I should say even though we had no clue about this, other people did, the people doing the University Group Diabetes Project (UGDP) and the beta-blocker heart attack trial (BHAT). They knew all about those things, the statisticians at NIH, but we really didn't. Anyway, now if you are looking at data in the course of the trial you use something called an O'Brien-Fleming analysis or one of several other ways of doing it. So, now everybody knows you have to do that. But, as I said, old publications may give you no clue about how this was done.

One of the principles that is established in many, many FDA and ICH guidance documents is that you have to account for all patients. Journals now won't take a paper unless you can account for all patients. One way that gets translated is in doing something called intent-to-treat analyses, making sure that everybody in the trial is counted, or at least that everybody who has data is counted in the trial.

But that too is something we didn't know about until the seminal experience of something called the ART, the Anturane Reinfarction Trial. I particularly like to talk about this because a colleague and I wrote a paper about it showing what had happened, but it was extremely instructive for us.

The Anturane Reinfarction Trial was an outcome trial, measuring survival. But, any trial can be manipulated by dropping patients who are inconvenient, who you decide were poor compliers or decide for a wide variety of reasons you would just as soon leave out of the study. The omissions characteristically look very plausible. No one ever does this for an obviously stupid reason; they always do it for a reason that looks sensible. But if it is done with the data in hand, then it is potentially biased.

Let me show you what the Anturane Reinfarction Trial showed, just as an illustration. It was in many ways a very, very well-designed trial. It was one of the first large outcome

studies that I am aware of that was done by a drug company as opposed to NIH or some other government. It was presented in The New England Journal of Medicine twice, once after an interim look and once at the final look. It had editorials from Gene Braunwald saying everybody should be getting Anturane if they have had a heart attack. Our analysis taught us a lot. It taught us about that cause-specific mortality assessment was very treacherous. It taught us about how you shouldn't have multiple endpoints (they did an unplanned six-month analysis that looked better than the overall results) But it was what the study showed about dropping patients that was most important. If you want to read what we learned, it is in The New England Journal from a long time ago.

Anyway, the ART was well-designed, placebo-controlled, and everything about it looked good. Patients were carefully selected. The study had some kind of monitoring committees but it isn't quite clear what they did, and how and whether this were blinded. These are the results they reported.

You can see that if you look at all cardiac deaths, they achieved near significance but if they looked at sudden deaths it looked really good. So the authors advocated looking at the sudden deaths. Just as a side bar, we discovered that the determination of whether someone died suddenly (a sudden death) or died for some other reason was largely bogus. If you died and were on Anturane your death tended to be due to a heart attack, called (AMI). If you died and were on placebo, on the other hand you tended to be called a sudden death. So, that was one thing. In addition to the overall analysis, they broke it down into first six months and second six months and you can see that the data keep getting better and better as you take further cuts of it.

All those problems were important but what I want to focus on one more. You couldn't tell this from the published report, but nine patients who had actually died in the course of the trial were excluded from the results as either ineligible or dropped because of poor compliance. The way

they knew three patients (2 Anturane and one placebo) had poor compliance is that when they died the pills were found in their room. Six patients were determined not to have been eligible in the first place because their heart attack was at 45 days instead of 43 days, or because of a variety of reasons. But they were allowed to complete the entire study and were only dropped later (after death) and they were not evenly distributed. All 6 of them were in the Anturane group.

So, when you put those back in the analysis you still have a weak trend. Who knows, Anturane might actually be good for you, but the nominal p value is now something like 0.2. Anyway, the whole thing was a revelation to us and to others. Our guidance in many places, and journals now, absolutely insist that you account for all patients.

It is worth remembering that it is not stupid to think that some patients should be dropped from an analysis. It is just that it is hard to know whether that was done in a neutral,

unbiased way. If it is not rigorously planned it can be biased. So, there could be rules that say if certain things happen I want to drop them; you could write that in a protocol. Many people would object to this, but if it could be considered. But to do it after the fact without planning, it is obviously biased. Now, similar things happened in the DESI program and I am going to recall an anecdote. I can't tell you what the drugs are but I remember this very well. This was some kind of pain medication. There were two studies, each of which showed no effect of the drug overall compared to placebo. In study 1, however, an analysis of the moderate and severe patients showed a statistically significant effect so the study was represented as positive for those. The very next study also negative overall, did an analysis of the mild patients, which showed an effect, and that was represented as favorable for that study. So, there is no end to what you can do with multiple subsets and analysis if you have free license. Anyway, we now understand that.

The active control, non-inferiority issue has been the subject of recent congressional interest, and it is a longer story than I can get into but in the distant past it was not uncommon-it was common actually to compare two drugs, find no significant difference between them and declare the two drugs of equal effectiveness. It is not self evidently a mistake to think that but it is in fact wrong and doesn't tell you what you hope it did. But the old literature on a lot of drugs has those studies in it.

So, it is perfectly sensible to think that showing no important difference between a new test drug and some drug that is established would be a way to show effectiveness, but the difficulty is, especially for symptomatic conditions, that drugs that work can't be shown to work in every study and the whole logic of the non-inferiority study requires knowing that the active control was effective in that study. I remember when I first realized that this was a problem. Other people knew about this before that, Paul Leber, who used

to run neuropharm., was railing about it as early as 1980 and Lou Lasagna actually had illustrations of why this was a problem going back to at least 1978. But what I remember is that we had finally managed to approve propranolol for the treatment of angina. It was difficult because there were dozens of studies and many of them couldn't show any effect on angina. But we finally concluded that enough studies had shown a favorable effect to approve propranolol for angina.

Then we got a proposal from Squibb to study nadolol, another beta-blocker, by comparing it with propranolol and showing no difference. But since we had known that dozens of studies had failed to distinguish propranolol from placebo, we finally realized, well, how can finding no difference between nadolol and propranolol tell you anything because you won't know whether this was a study that could have found a difference between drugs that work and those that didn’t or was a study that couldn't show such a difference. We realized that in such cases active control trials

couldn't be used and started pointing this out publicly.

The basic idea of a non-inferiority study is that it tries to show effectiveness by showing that the new drug is not worse than the old drug by a certain amount, and that amount can never be larger than the whole effect of the old drug in this study. So, if the old drug has an effect of 10 and you show that the difference between the new drug and the old drug is less than 10, then the new drug has some effect. That is the theory. The way you do it this is to show that control minus test is less than some margin where, again, the margin can't be any larger than the whole effect the control drug had in this study. The trouble is you don't measure the effect of the control drug. You have to deduce it from the past and in an awful lot of cases you can't be sure that it had that effect, and that is the trouble. If you don't know that, then showing no difference doesn't mean anything. It could mean both drugs are effective. It could mean neither drug was effective.

I am just going to show you an example of a drug that works but that couldn't be shown to work. In fact, in conditions like depression, pain treatment, allergic rhinitis, irritable bowel syndrome and angina you quite regularly have studies that are of good design, as far as anybody knows, but that can't tell the drug from placebo. In that setting you can't use the non-inferiority design. I am just going to illustrate this with some depression studies.

But I should tell you, even though this example is particularly suitable and that is why I chose it, we know that about half of the placebo-controlled trials of effective antidepressants-all the drugs we know and love and that are effective cannot distinguish drug from placebo. That failure rate has persisted from the '80s to the present.

What this table is, is an illustratiom of why non-inferiority is not persuasive. These are six trials of a drug called nomifensine that was withdrawn because it caused hemolytic anemia but

was an effective antidepressant. The studies are all three-arm trials comparing the new drug, nomifensine, imipramine, a standard tricylic, and placebo, but in this slide I am not showing you the placebo yet.

This is their baseline Hamilton Depression Scale, a standard measure. The four-week values all show a nice improvement and the results for the nomifensine and imipramine are and the same they are right on top of each other and look identically effective. So, if you believed in the concept of non-inferiority trials, even though some of these trials are kind of small, this would be pretty persuasive.

The trouble is only one of the trials was capable of telling anything from anything. If you now look at results in all 3 groups, it's clear that the drug and placebo effects are the same in every study except the fourth. This teeny-weeny study with seven people per group was the only one that was capable of distinguishing active from inactive drugs. As I said, our experience in

depression has been that about half of all trials can show anything.

So, you can only use the non-inferiority design where you are really, really, really sure that the control drug will have an effect.

There are two more things to talk about. I want to talk about the number of studies that are needed and then the use of studies where you don't quite have all the data. Both of these matters are addressed in our guidance on evidence that I mentioned before. That guidance was written at least partly in response to FDAMA, allowed the use of a single study under some circumstances this was our attempt to describe what those circumstances were.

The guidance also addressed the issue of the quality of evidence, when we would use less detailed reports and when we would use literature. So, it is a guidance document that, if you are considering using older data, you definitely need to look at.

The first thing it did was describe all of the situations in which you might only need one new study of the particular drug, dosage form, strength or whatever that you were trying to market but there were other data that would support it. These are relatively straightforward examples. So, what it says, and this shouldn't surprise anybody, is that if you have a study of a different dose, regimen, dosage form, and so on, those count too. Those support your new study. In fact, the whole DESI review was really done in a sort of generic way. Studies of a wide variety of different products, sometimes different salts, were all thrown together to see if enough data could be developed. So, studies in other phases of the same disease; studies of mild pain; studies of moderate pain; studies in different populations. You can gain information from both a combination study and from a study where you use the drug alone. They both show the effect of the drug. All of these things can be joined to provide evidence.

This is more debatable, but in some cases

one might be persuaded by one study in one kind of arthritis and a second study in another kind of arthritis. Those cases would be debated and would have to be discussed with the division but this guidance says it is possible.

Sometimes you could be studying two different endpoints. Again, how often this is going to apply here I don't know, but when we first approved enalapril for heart failure we had one study of outcome, survival, and another study that showed improved exercise tolerance. The general principle, though, is that if you show something that is meaningful in one study and show something that is slightly different but also meaningful in another study, it is possible that that could represent the two studies that are needed. When and whether a surrogate endpoint might be part of that could also be important but, again, for symptomatic conditions I don't think that is a major worry.

A more difficult case for us, one that

probably needs further development, is whether under some circumstances the known pharmacologic effects of the drugs can provide support for actual clinical evidence. I won't discuss that in great detail but if anybody thought he had a case like that, I think you have to take it to the review division and see.

Now, the document also describes at least some degree of flexibility with respect to the level of submitted detail. You have to remember what we are used to. We are used to everything. We get certain selected case reports and then any other ones if we want them. We get listings of every adverse effect, every measurement, every laboratory datum. We usually get everything in a very detailed protocol that describes everything that was done.

But, first of all, older studies didn't always have protocols that did that. Second of all, the literature hardly ever has that level-well, can't possibly have that level - of detail. So, the question is when can we give a

little and accept a little less detail, and this document describes that.

For example, there may be a publication that may not give much detail but sometimes the protocol is available. Well, that helps the credibility of that study a lot. So, this isn't a cookbook by any means but it does say it is possible that we rely on somewhat less detail.

The things that make literature persuasive in the absence of the usual amount of detail are multiple well-designed studies by different investigators and unusually detailed reports (but, again, don't look for that from the '60s); readily available and appropriate endpoints, that is, things that don't involve too much judgment; robust results by a protocol-specified analysis, if you can find the protocol-specified analysis; and there is something about conduct by groups with a good track record. I don't know how much one wants to make of that but it does say that.

That is it. So, I will be glad to answer questions later. That is probably more than you

wanted to know. I guess the last thing I would say is that the review divisions are always ready to go over the data that people think they have and want to discuss in meetings with us and we are glad to have conversations about these things.

**Question and Answer Session**

MS. AUTOR: Thank you, Bob. At this point we are going to have a question and answer session for about 45 minutes. So, for those people who see their names up here, if you could please join me on the stage, that would be great. We have envelopes with the questions that have been submitted so far. I think what we will try to do to keep organized is have each of the speakers, to the extent that they can, take the questions that have come and try to address some of those to begin with. Then we will see how many more questions we have and how much time we have left and what additional questions we can take.

I guess, since I spoke first, it leaves me with answering questions first. So, let me try that. The first question in my stack is:

*What are my responsibilities if I think my product is GRAS/GRAE or grandfathered? Who do I submit my evidence to and what do I submit?*

There are two different answers to that. If you think your product is grandfathered, there is actually a regulation for you to look at. That would be 21 CFR 314.200 subpart (e). You can look at that regulation and it spells out what you have to submit. It comes to the Office of Compliance. I believe if you look at the appendix to the Compliance Policy Guide on Marketed Unapproved Drugs, you will also find citations for a couple of cases on the grandfathering standard. So, that is the easier part.

I would suggest that if somebody thinks their product is, in fact, GRAS/GRAE that they should submit that information to the Office of Compliance. I would say submit it to the same place. There is no requirement that you do that but, considering that the agency is on a regular basis looking at all unapproved drugs on the market and evaluating those for potential enforcement action, I think if you think your product is

GRAS/GRAE and, therefore, shouldn't be an enforcement target, that is the kind of thing you would want to tell us about. So, again, you could submit that information to the Office of Compliance.

Then, there is sort of a series of questions here which I think come down to what will FDA do to accelerate enforcement against unapproved products once a sponsor submits an application for approval or obtains approval.

There are a couple of subsets there. The first question:

> *Is it allowed to continue marketing an unapproved drug while a company is working with the agency under the IND or ANDA process? If so, for how long?*

This is an important point and I know some of the folks here from the media had the same question. The approval process and the enforcement process are largely running independently. Filing an application for approval is certainly not a trigger for enforcement and it is also not a shield from enforcement. We need to be constantly

evaluating what the proper targets are for enforcement based on the priorities set forth in the CPG. Filing an application isn't going to change where you are on that list but, on the other hand, if you have an application pending that is also not going to be a defense if we end up deciding to take enforcement.

That being said, probably if something was about to get approved it wouldn't necessarily be the best use of our enforcement resources but, again, just putting an application in doesn't change where you go in the enforcement queue. That is going to depend on the priorities laid out in the CPG.

Then, the question was -I will read it.

*It took the FDA two years to clear the market for the approval of quinine sulfate. Wouldn't there be greater incentive for companies to try to get approval for an unapproved drug if the enforcement was accelerated? Would FDA commit to a three-month enforcement period?*

We certainly recognize the need to accelerate our enforcement and we are committed to doing that. I don't think we can commit to any specific time period. There are a lot of factors

that dictate when we can take enforcement action, including what other priorities we might have, what the process is through the agency, what the other potential enforcement issues might be. But, again, we recognize the need to accelerate that. We recognize the need to follow through on that incentive and those statements in the Compliance Policy Guide, and we will do everything in our power to make that happen in the circumstances where it should happen.

This one asks:

*In what manner will you accelerate injunctions against unapproved drugs.*

I think it asks more broadly about enforcement. I think we are just redoubling our efforts and our resources devoted to this, and I think that we will be accelerating in whatever ways we can, and I think we have to look at what remedies will really change the situation and encourage companies to come in and get approval. I think Dr. Galson addressed the question of whether we should be looking into reimbursement of these

products. We also have traditional injunctions, Federal Register notices, warning letters and anything else that we think is appropriate in the circumstances. We are serious about working with you to get approval. We are also serious about tackling this problem, and we need to get to a point where companies are being proactive about compliance. So, I hope that addresses that question.

This question says:

> *In the case where there are multiple marketers of the same unapproved new drug product, when a marketer submits an NDA and FDA is proposing exclusivity, at the same time FDA indicates that the FDA will exercise enforcement discretion for unapproved products, permitting them to remain on the market. How does FDA plan to rationalize granting exclusivity while also permitting non-submitters to remain on the market?*

I think that goes to the balance structure in our Compliance Policy Guide with respect to exclusivity if we take action against unapproved versions of an approved drug. The CPG talks a lot about what the appropriate grace period should be in balancing the factors but, again, if somebody comes in and gets approval for a drug that other

companies are marketing without approval that is an enforcement priority for us, and we hope to create situations where our enforcement action is timely, such that it creates a reasonable incentive for companies to come and get approval; that it makes it worthwhile to do it.

There is a question about compounded drugs and the relationship to this discussion of compounded drugs. This meeting is not about compounded drugs. Compounded drugs are really a separate issue that we are not talking about here today and there is a separate compliance policy guide on compounded drugs-the same office, different compliance policy guide.

One question is:

*How can a company use the presence of a current pharmacy compounded to their advantage during the NDA process?*

Maybe folks down here could talk about that. My guess is that the answers are the same as the extent to which a company can use any other marketed drug, and history of that as evidence in support of an application is going to depend on

literature; it is going to depend on the evidence that you have. Just the fact that a drug is out there being compounded by pharmacies and may have been sold for some period of time I think is probably not going to be a great benefit in the application process. Does anyone else want to say a word on that? We can come back to it later.

The next question:

*Why are these products illegal?*

[Laughter]

That might be one to take to Congress.

*If the product was initially marketed in the '50s with approval of the FDA, without the necessity of an NDA, so long as the product is marketed under a prescriptive legend and the prior compliance policy guide stated that the FDA would eventually review the product to see if an application would be necessary, why is the product illegal?*

I can't speak to those specific circumstances. I don't know of any circumstance in which - well, I should say there was a situation

where the agency had issued letters allowing marketing of certain products without applications. Those letters were revoked and there is a long discussion of that in the appendix to our compliance policy guide. So, that may be what this situation is getting to. The former compliance policy guide has also been revoked and that compliance policy guide spelled out some steps the agency was taking to deal with unapproved drugs.

Now, there are different interpretations of that compliance policy guide. My interpretation of it, frankly, is that it was basically all done and, therefore, not really of any use. Other people saw it as a statement that we wouldn't get to this until we got to that and wouldn't get to the next thing until we got to the prior thing, and it created a lot of confusion, a lot of difficulty. So, the prior compliance policy guide is gone and so that is why that doesn't affect the situation today.

*Is the marketing of unapproved drugs illegal? Is the selling of unapproved drugs*

*illegal?*

If a drug needs FDA approval and doesn't have it, then the shipment of that drug in interstate commerce is a violation of the Federal Food, Drug and Cosmetic Act. There are other ways in which handling of that drug could also be problematic but the basic answer is yes, if a drug needs FDA approval and it doesn't have it then it is illegal to be dealing with that drug.

Let's see, I can maybe address this to Bob Temple.

*In cases where an unapproved new drug makes unsubstantiated label or advertising claims will DDMAC pursue enforcement independent of any potential enforcement by the Office of Compliance?*

DR. TEMPLE: That is a good question because they have no labeling to violate.

[Laughter]

I guess if we thought that there was an important public health implication of what was being promoted, for example promoted as an alternative to something that was life-saving, we would consider it. I don't believe it has come up.

That is sort of a standard I would use for dietary supplements too, but I am not sure we would do that either.

MS. AUTOR: Thanks, Bob.

*Is there a list of unapproved drugs which you intend to remove from the market? Will you accelerate removal of unapproved drugs this coming year, and how many will you remove?*

I addressed some of that. There is not a publicly available list of unapproved drugs that we intend to remove from the market. There is not really even such a list. We are constantly evaluating potential targets of enforcement priorities based on information we get from consumers, from physicians, from pharmacists, from MedWatch, from our in-house scientists, and from every source that we can, to decide what is the next appropriate target but it fluctuates and varies depending on the information we have. We are trying to use our resources to do the best we can to protect the public health so that is how we choose what our next enforcement target should be. We do intend to accelerate removal of unapproved

drugs this coming year. I can't tell you exactly how many we will remove. We intend in general to accelerate our enforcement in this area to really start to make real progress and get to the point where all drugs we know are up to current standards of safety, efficacy, quality and labeling.

Somebody asked about the list of the DESI drugs, especially the unfinished 20 drugs. It is actually a little bit less than 20. The thing I would say about that list is that every drug on that list is one that was initially found to be ineffective by the agency. So, if you have a drug on that list, then I think you should be thinking hard about whether you want to continue to market it even while the DESI proceeding is pending. If you don't have a drug on that list, I am not sure you need to see the list. But we will look into that. It might be something that the agency could make available but, again, DESI is basically done and the only lingering DESI products are ones that were initially found to be ineffective by the agency and there may still be hearings pending or

other things like that. But, basically, DESI drugs should at this point be off the market, with those limited exceptions of the things that are pending.

Let's see, (next question)

*Will FDA prioritize enforcement actions against unapproved new drugs in situations where under the OTC Drug Review FDA has indicated that drugs containing specific ingredients are unapproved new drugs that require NDA approval?*

I think our priorities for enforcement are those set out in the CPG. If there is something somewhere which indicates that something should be a higher priority under the priorities in CPG, then that would be what we would be looking at but, again, the priorities are those set forth in CPG.

*How will FDA determine which categories are the highest priorities to target?*

I think we talked about that.

I don't understand this last question:

*What will the requirements be? Will you need a complete efficacy program?*

If that talks about approval and what you need for approval, you know, I think Bob started to talk about that and we can talk more about that.

Gary, do you want to volunteer to go next on questions?

MR. BUEHLER: I was trying to give a couple of mine to Bob but he wouldn't take them!

*Can a drug product be designated as a generic drug if there is no reference listed drug due to the fact that both drugs are identical, related or similar to a pre-'62 drug?*

No, we don't have any identical, related or similar products coming in anymore. That was sort of an early 1980s thing that we used to do. Right now, as I said in my talk, you need a reference listed drug. You have to compare to the reference listed drug unless you have a suitability petition.

A lot of these questions are kind of similar. I should have given this one to Bob.

DR. TEMPLE: Sometimes the reference listed drug may have dropped off the market because of lack of commercial interest, in which case it still could be in again. Right?

MR. BUEHLER: Bob said that at times the reference listed drug drops off the market due to whatever considerations. At that point, if it was

an approved reference product at that time, you could come back. You would have to petition the agency, put a petition in to us and ask the agency to make a determination as to whether that product went off the market for reasons of safety or efficacy. We would publish that finding and if it did not go off the market for reasons of safety or efficacy you could bring an ANDA in again for that particular product. We may require additional studies or additional labeling depending upon what the product was and, you know, if there were some considerations that sort of edged the product off the market. So, we would have to make that determination, and we are trying to publish the conditions in the determination now too.

*Is an ANDA possible in the absence of an approved NDA or available RLD?*

That is sort of the same question and, again, you need an RLD. This is a similar question.

*What if it is a pre-'62 drug? Can there be*

*generics of unapproved drugs?*

If it is a pre '62 drug it would be a DESI drug. If the drug cleared the DESI process it would have an approved RLD that you would come in against. If the drug didn't clear the DESI process it would be in that sort of bunch that still needed to have whatever clinical verification to get it out of the DESI unapproved product and, therefore, it couldn't come in as a generic.

Can one unapproved prescription drug be considered a generic to another unapproved prescription drug in the absence of data establishing bioequivalence? In other words, is there a different definition of generic unapproved drugs? No. No and no.

[Laughter]

This one I actually did ask Bob and we weren't able quite to figure out what the questioner was getting at. It says:

*When the RLD does not undergo clinical or bioequivalency testing why does a generic product for the same drug need to demonstrate bioequivalency to an RLD that did not undergo any clinical testing?*

We were trying to figure out what RLD there would be that didn't have some clinical testing to get approved. Even DESI products, or whateverB-you know, we have a certain standard of safety and efficacy for a product to get approved so I am not quite sure what we are getting at here but I think that whatever the questioner wants, I don't think they can get.

[Laughter]

*Is an IND required for conducting a BE study? If not, what about a clinical efficacy study for a topical generic? Are there potential safety concerns for ANDA products?*

INDs are not required for bioequivalency studies except for a few exceptions. If you have a cytotoxic drug or, for whatever reason, you have to increase the dose by more than threefold, the highest approved dose by more than threefold then you would need an IND. I think there may be one other condition. They are in the regulations I believe, these IND exceptions.

Now, the topical products that I mentioned, the pharmacodynamic studies that we

require for topical products are considered bioequivalence studies. They are bioequivalence studies with clinical endpoints. So, these are bioequivalence studies and, as bioequivalence studies, they don't require an IND. They are not considered efficacy studies and when you put them in you have to compare your test product with the reference product in your study. The comparison is not an efficacy comparison. You should also have a placebo in the study to make sure that your study is sensitive enough to pick up changes but they have to be compared to the reference product. You also have to meet the bioequivalence goalposts, both the lower and the upper goalpost. You have to be in the 80-125 range. So, actually, these studies are more challenging than the actual efficacy studies that the reference product had to do because all the reference product had to do is show that it beat placebo, whereas, you have to show that you are equivalent to a marketed product within a certain range of equivalency.

This one is exactly the same question.

The questioner says that:

*For a bioequivalence study for guaifenesin 600, 800, 1000 and 1200 mg, Humibid 1200 mg is the RLD. It is not available in the market and so what should we use for the RLD?*

You can notify us that this is not available in the market and we will research that, and we will change the "Orange Book" to what would be the highest strength that is marketed. If you like, you can use the highest strength and then you are able to waive down to the 800 and the 600 as long as your product is composition proportional and your dissolution is within the same range. You cannot waive up though. So, at some point, if Adams puts its 1.2 gm product on the market and you want to market that you would have to do another bioequivalence study to the 1.2.

*Please clarify the situation in which a DMF would be required or not required for inactive ingredients. Would you consider historical stability data when assigning a shelf life?*

I asked a number of people in the audience before I came up here about DMFs for inactive ingredients. I don't believe we get many DMFs for

inactive ingredients. Most of the time inactive ingredients are qualified through the IIG, the Inactive Ingredient Guide, where you can see the maximum levels of a particular inactive ingredient that, you know, would be acceptable in an ANDA. Now, if I am missing something, you can come and get me at the break, or whatever, and I can try and clarify that. As far as historical stability data, I mean, you know, we will look at it but we really want you to have stability data on the batch that you submit to us and the batch that you have done the bioequivalent study on. To us, everything sort of emanates from that batch so we would want to see stability data on that particular batch in your application. I think I am done.

MS. AUTOR: Okay. Moheb?

DR. NASR: I have only one question. I think my presentation was very clear!

[Laughter]

So, unlike other distinguished members of the panel, I have one question. The question is:

*Does the FDA consider different specifications for different drug products?*

Yes, we do. I think in general, for the sake of clarity for this audience, you can consult publicly standards for oral solids to know what kind of expectations we have but, obviously, for different drug products there will be different requirements depending on the product.

Two important things, one is that in addition to end-release testing we also look at the manufacturing process and in-process testing and other quality assurances. That is very important and that is why we are interested in seeing some more applications to apply our standards.

The third point is that the questioner really did a good job by defining what specifications are. So, it seems like he understood that part fairly well. I am very pleased.

MR. BUEHLER: There was one question I think I didn't address. It was about the safety in the BE studies. Yes, you do have to report safety in the BE studies, similar to the clinical requirements. We do want to know if any safety

issues come up. Thankfully, at least from my point of view, we don't see a whole lot of problems since these products have been marketed for a number of years.

DR. TEMPLE: I have one thought about the advertising question before. A lot of these unapproved drugs actually have an approved version in the marketplace and that gives you some idea of what the appropriate claims might be. I would say if there were something markedly at odds with the ordinary claims for the same molecule, it would catch our attention if anybody did that. Most of these things aren't highly promoted, however.

I have two questions. One is:

*If an unapproved drug has been on the market for forty years will two adequate and well-controlled trials and a full preclinical package be required?*

We should probably leave the second half of that for David to discuss in the afternoon. But the answer to the first part is you need substantial evidence of effectiveness and that ordinarily would require two adequate and well-controlled studies. The Hynson, Westcott and

Dunning decision has a terrific set of speeches by people about how long marketing doesn't really tell you anything, and we don't think it does. It probably tells you something about safety, or it might if it was extensive, but it doesn't tell you that the therapy works. So, that is pretty clear.

The second question is:

*What are the clinical trial requirements under 505(b)(2) to demonstrate safety and effectiveness in general and for topicals?*

Others may want to comment on this, but approval requires the same level of evidence that you need for any other approval. It is just that you get some of it from elsewhere. So, it depends. For example, we have had situations where we thought new controlled-release dosage forms of, say, antihypertensives needed some evidence of effectiveness; that bioavailability assessments weren't sufficient. We have, however, given the knowledge about the molecule, thought that a single study showing sustained effect over time was sufficient. It probably didn't have to be as long as the trials would have been if it were a brand-new molecule. So, the data is what people consider necessary.

For topicals, again, Gary already said that what you are doing is doing bioequivalence because you can't measure blood levels for topicals. He has described the standard there. If this were a 505(b)(2) where it was a different salt, or something like that, we, again, might take into account the fact that there was a lot of information available on the other salt and require only a single study. But I would say it gets negotiated and discussed case-by-case. John?

DR. JENKINS: Yes, in general when we get a 505(b)(2) application you are referencing another product and you are not eligible to be an ANDA. So, kind of the rule of thumb is that we look at how you are different from the product that you are referencing. You are referencing a finding of safety and effectiveness for a reference listed drug or the product that you are referencing in your application, and we look to see, okay, how does our finding about that product relate to what we need to know about the approval of your product. So, it really becomes a case-by-case analysis of

how much can we take from our previous finding of safety and effectiveness for the reference product and how different is the product that you are proposing to market.

To give an extreme example, perhaps you are referencing an oral product but you want to give it by the inhalation route. Well, obviously, you can learn some things from our previous finding about safety and effectiveness of the product given by the oral route but there is going to be a lot of new information that is going to be needed about the safety and effectiveness, and also the quality and purity of the product given by the inhaled route. So, it really is a case-by-case analysis, looking at what you are referencing; what you are proposing to market; and then we have to decide what our data needs are to assure that the new product is safe and effective.

I would just like to say my presentation this afternoon is going to be so clear I don't have any questions from the audience at this point.

[Laughter]

I will pass the microphone on down.

MS. AUTOR: Well, I actually neglected to introduce Dr. John Jenkins. He may not need an introduction, but John is the head of the Office of New Drugs, which is the office at CDER responsible for reviewing and approving new drugs. I will tell you his full bio later when he comes to give his crystal-clear presentation, but in the meanwhile we appreciate his help with the questions.

DR. TAN: I have five questions. The first is:

*Is there any exclusivity afforded to companies amending the OTC monograph?*

No. That is an important distinction. There is no exclusivity given for the OTC monograph pathway.

The second question:

*Can you address the timing and number of OTC monographs expected to be finalized in the next one or two years?*

I can only control the writing part of it. That is what we do. After we write it and draft it, it still has to go through clearance and

possibly HHS and the Office of Management and Budget. So, we really can't give you a precise date for when these will be finished. Twice a year there is a unified agenda that is published that gives an estimate for when we plan to get these monographs done.

MS. AUTOR: Can I just actually clarify one point there? I am not exactly sure how the question was phrased but there is no legal exclusivity for a drug that comes to market through the OTC monograph process, as Reynold just said. It is possible that we would consider as a priority for enforcement some drugs that are marketed either in violation of a final monograph or if someone goes through some other process to be marketed OTC, then we would perhaps consider that as an enforcement target. There may be some sort of de facto exclusivity that could come even when a drug comes to market OTC. My office handles unapproved OTC drugs, drugs in violation of the monograph, as well as unapproved Rx drugs. Those are always considered as potential targets for enforcement.

DR. TAN: The third question:

*Can ibuprofen be marketed under OTC since there is a pending monograph, or do we need to have an ANDA filed before it can be marketed?*

Ibuprofen needs to be marketed under an NDA or an ANDA at this point. This is a good question because if you follow the decision tree, it would lead you to believe that you can market ibuprofen under a pending monograph. But this is a special example. We published a proposed rule, that has yet to be finalized, that says that you can't under the monograph pathway. So, you need to wait until the internal analgesic monograph is made final.

*Would you please provide an example of the citizen petition deviation?*

Yes, I provided an example of the antacid final monograph. I actually got a comment from at least two or three doctors that were commenting on it. For example, the antacid final monograph allows sodium bicarbonate, baking soda, to be used as an antacid and a couple of doctors were concerned that people were taking huge doses of sodium bicarbonate and essentially just blowing up

their stomachs. These doctors requested a warning that says something to the effect of don't take on a full stomach. So, that is an example of a warning they would want included in the final monograph and you could submit a citizen petition to get that warning included.

*Are drug entities listed in a monograph always assigned OTC status even if the dosage form and dosage strength are different?*

I think what you are getting after here is - well, let me explain it this way, again, the monograph is for active ingredient and the conditions of your product. So, if it is under an active ingredient then you have requirements for dosage strength; sometimes dosage form. So, if your product differs in any of these conditions, then it may not be in the OTC monograph.

If this question is after whether something that is covered in a monograph can be marketed or qualifies as Rx status, no, it can't. So, if you have something with a dosage strength linked to the indication that is OTC, it certainly cannot be both OTC and prescription.

This question says:

*There are NDA products that are required to meet OTC efficacy requirements for approval. Why cannot these active ingredients be included in the OTC monograph?*

The problem with that is that you have to consider the OTC setting for the product. So, even if you have products that are allowed for an NDA you have to consider whether the conditions of use in an OTC environment change the requirements. Usually that is for safety.

*What is the best pathway for resolving a deviation from a tentative final monograph?*

I think you are out of luck there. The tentative final monograph is a proposed monograph there so, because the citizen petition and the TEA can be used to amend any step of the procedure, you can use a citizen petition or the TEA to amend the monograph even if it just at the tentative final monograph stage.

This one is a sentence that says status of OTC monographs not yet finalized, question mark. To me, that is not really a question. I think what they are after here is how do you check on the

status of an OTC monograph. In my talk check the industry web link and that links you to the rulemaking history, and you can find whether the OTC monograph is at ANPR stage, TFM stage of the final monograph stage. That does it for me.

MS. COLANGELO: The first question I have here:

*Is FDA willing to approve more than one 505(b)(2) application for the same marketed unapproved product?*

The answer here is maybe. Under certain circumstances that could potentially occur, but there are many things that affect the approval of a (b)(2) application, including existing patents for the active ingredient, as well as any existing exclusivity that may be unexpired. You should also keep in mind that once the first (b)(2) application is approved, if your product is eligible to be a generic product it must come in under the generic pathway.

The next question actually has already been addressed several times. It says:

*For an ANDA or a 505(b)(2) do you have to do human clinical trials for a topical product?*

I think you have already heard about some of the trials that you would likely need to do if you are comparing yourself to a product that is already approved either in the ANDA process or in order to rely upon a previous finding under the (b)(2) process. You would likely need pharmacodynamic data to support the equivalence of your product or to build that bridge, presuming that your product is not systemically absorbed.

A question reads:

*Talk about the use of paper NDAs for preclinical and clinical filing requirements.*

I believe this is in reference to what we used to call paper NDAs, which is not what I was referring to in my talk. When I said paper NDAs I truly meant NDAs that were submitted using paper versus those that come in on electronic media. Paper NDAs no longer really exist. This was something that we had prior to the implementation of 505(b)(2) and they are kind of subsumed in that. But the filing requirements for any NDA are going to be do you have the information that we require in order to provide us substantial information to

complete our review on whether or not you have enough evidence to support marketing under your proposed indication and conditions of us.

*For a 505(b)(2), how do you reference the FDA findings of safe and effective in an IND application?*

The answer to that is you don't. There are no findings of safety and efficacy contained within IND applications. But if you are talking about the information that is contained in the IND, the NDA application is actually a summary of all of the information that you have gathered over the course of the IND, and our findings of safety and efficacy actually would be summarized in the product labeling for the approved product. So, that would be where you would go to find the information.

Lastly, there are two questions here regarding the

*…requirement for what we refer to as the animal rule or animal efficacy rule specific to products to use as counter-terrorist measures.*

There are regulations that allow us to approve a product solely on animal studies for products that are designed to be used as

counter-terrorist measures where it would not be ethical to do clinical human trials. Those regulations are in 21 CFR in what we call subpart (I) of section 314. Bob or John, do you want to say anything more about that?

DR. TEMPLE: Well, it is something where you would definitely want to come in and chat. These are never, never simple and there is a wide variety of commitments that you make at the time, and it needs data from two species. It is worth talking about. It is doable if it is really something where the thing you are trying to prevent damage from can't be tested in humans, and there are a lot of examples where you wouldn't want to expose people to something. That is what the rule is for, but it is definitely worth a conversation.

I have two. The first:

*For an unapproved drug sold under a prescription legend and having many years of safe use, can a pilot efficacy trial be conducted without an IND?*

The answer is no. There is an exemption to the IND requirement under 312.2 for certain

studies of legally marketed drugs. Other than that, all drugs are investigational so they need an IND. So, in this situation you would need an IND even for a small pilot study.

*How do you develop the clinical requirements for a product previously approved by the FDA but that did not require a clinical study?*

That is a little bit like the question Gary was grappling with. I would have to know what the example was where we approved something without a clinical study. There certainly are products that have sort of minimal clinical studies-replacement solutions, dialysis solutions, some of those things-and we have approved 505(b)(2) applications on the basis of their contents in some cases so it would meet the same standard where that was considered sufficient evidence of effectiveness. I think we need to see more details here. I can't answer in a general way. Most of the time there are studies. It may be a study of a surrogate endpoint or something but there are usually studies.

MS. AUTOR: Gary, do you have additional

questions? I have a few here I could touch on.

MR. BUEHLER: I have a few too.

MS. AUTOR: Okay, but we are almost out of time.

MR. BUEHLER: Do you want to do yours?

MS. AUTOR: Well, I will be here this afternoon too so why don't you go ahead?

MR. BUEHLER: OK

*Does FDA review approve BE study protocols, especially when the CRO is located overseas and never been inspected by FDA?*

Well, the standard protocols for solid orals, or whatever, we don't really review those protocols. You can request bioequivalence requirements and we will send them to you in letter form. We are trying to get them up on the web so people can actually access them on our website for bioequivalence requirements. For more complicated studies, especially studies with clinical endpoints, I would recommend that you request us to look at your protocol and provide you guidance before you start these sometimes very expensive studies.

The second part of the question is:

*How long does it take?*

I am very sorry to say it takes quite a long time sometimes. You know, ten months to a year is not unusual. We got 1,800 letters last year and we are still sorting through them.

Someone asked about topical nasal sprays. We don't have nearly enough time for me to go into what is required for a topical nasal spray. I would send us a letter and submit the specific questions that you have for the specific drug because it varies depending upon what topical nasal spray product you want to get as an ANDA.

Drug-device combos, metered-dose inhalers we accept in the Office of Generic Drugs. You know, we will accept drug-device combos if they are approved products but we will certainly look at the device very carefully. For metered-dose inhalers I believe the review of the device is at least as onerous as the review of the actual drug product. If it is a device that is different from the RLD you are really asking for some problems. So, we

will certainly review that. We will possibly consult it to CDRH if need be.

Orally administered products that act topically - I assume they are meaning like sucralfate and mesalamine and those things - we have had a number of questions about products such a mesalamine, the products for colitis and such. Each one of these has their own bioequivalence recommendations. We have had to carefully research these products in conjunction with the New Drug Division and each one of them has its own set of bioequivalence requirements. So, again, I would suggest that you send us a letter and request the requirements.

DR. NASR: I have a few questions that I will be happy to discuss in the afternoon. I think they are very simple. I am just being challenged about my earlier statement.

MS. AUTOR: Well, with that statement, why don't we break for lunch? We have an hour and a quarter for lunch. Please be back here so we can start at 1:45 with our afternoon presentations.

Thank you.

[Whereupon, at 12:30 p.m., the proceedings were recessed for lunch, to resume at 1:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

MS. AUTOR: I am going to introduce all three speakers all at once so you won't have to hear too much from me. There are three speakers on the topic of demonstrating product safety. The first one is going to be John Jenkins, whom you met during the Q&A. John, as I mentioned, is the Director of the Office of New Drugs. John joined FDA as a medical officer in the Division of Oncology and Pulmonary Drug Products in 1992. He subsequently served as Pulmonary Medical Group Leader and Acting Division Director before being appointed as Director or the newly created Division of Pulmonary Drug Products in 1995. Dr. Jenkins became the Director of the Office of Drug Evaluation II in 1999 and served in that position until he was appointed to his current position in January 2002. Dr. Jenkins is Board Certified in Internal Medicine and Pulmonary Diseases.

John will give some overview comments, followed by David Jacobson-Kram, who is going to talk about demonstrating preclinical safety. Dr.

Jacobson-Kram joined the Office of New Drugs in 2003. Prior to FDA, he worked in the private sector, holding such positions as the Vice President of Toxicology and Laboratory Animal Health and serving on the faculties of the George Washington University Medical School and the Johns Hopkins University Oncology Center. Throughout his career, Dr. Jacobson-Kram has published extensively on genetic and molecular toxicology.

Also presenting on the subject of demonstrating product safety in an NDA, Dr. Robert Meyer, who is Director of the Office of Drug Evaluation II. Bob has been the Director of the Office of Drug Evaluation II since 2002. That ODE is responsible for the regulation of endocrine/metabolic, pulmonary, allergy, rheumatologic, analgesic and anesthetic products. He is involved in a number of center and agency level activities such as chairing the agency's risk assessment guidance working group and the drug safety oversight board. Dr. Meyer began his career with FDA in 1994 and I am sure you will join me in

welcoming this illustrious group to talk to you about demonstrating product safety.

**NDA/Demonstrating Product Safety**

DR. JENKINS: Thank you, all, for coming to the session today. I hope you are finding it useful. I am going to just spend a few minutes doing some introductory overview comments on two topics. One is about the Office of New Drugs and one is about general comments about demonstrating product safety.

If you have your decision tree and if you end up in the green parts of the decision tree you are going to be coming to the Office of New Drugs. We, in the Office of New Drugs, are responsible for the oversight of investigational drugs and we are also responsible for the approval decisions on the new drug applications. So, while I am sure most of you hope you are going to be in the blue or the yellow or tan squares, if you find yourself in the green squares you will be coming to see me and my staff.

We are the largest office in the Center

for Drugs. We have over 700 people. We are actually organized into clinical review divisions that are based primarily on clinical sub specialties of medicine. So, we have 15 reviewing divisions that you will be interacting with for the most part that are allocated based on clinical sub specialties, such as Division of Cardiorenal Products or the Division of Neurology Products. We also have a division that is devoted to the OTC monograph. So, those of you who fall into the yellow parts of the table will also be up in the Office of New Drugs. We also have the division in the OTC office that deals with NDA OTC products.

We do have the regulatory authority for not only overseeing your IND applications if, in fact, you need an IND but we also make the eventual decision about whether your product meets the evidence standard for approval. Then, we are also involved in monitoring your product after approval. So, we have regulatory authority for the product all the way through its life cycle, from clinical investigations, NDA submissions and approval and

then in the post-approval realm.

Those activities are conducted in coordination with many other offices within the Center that have expertise in various areas, and it is also done in cooperation, for example, with the Office of Compliance, particularly in subjects relating to unapproved drugs.

Moving on to some general comments about demonstration of product safety, it is important to remember that what we are talking about is meeting the standard that is called for under the statute for safety for the product, which really talks about that the product is safe and effective when used for its intended use based on the indications and the directions that are included in the labeling. Many of you know and probably hear often from FDA that there is no such thing as a truly safe drug. I remember from my medical school pharmacology days that we were told that if a drug had no adverse consequences it also didn't have any benefits. So, it is really impossible I think to find a drug that is truly safe and, unfortunately,

that confuses people because we all can talk about drugs being safe and effective but there are no truly completely safe products.

When we look at demonstration of safety for a product we are looking at the intended use and factors that go into the intended use such as the chronicity of the use of the product and the population that will be using the product. Those all factor into what we expect in the application so that we can assess the safety of the product for its intended use.

We approach it by looking for data from several different areas. One is the preclinical arena which will be both laboratory tests as well as animal testing. You will hear more about that from Dr. David Jacobson-Kram in a few minutes. We then look at the safety data that are derived from the controlled clinical trials and also the uncontrolled clinical trials that are conducted during the IND and as part of your submission for the NDA. Then, of course, we look at other sources of information, including information from

post-marketing surveillance if a product has been on the market. You are looking at spontaneous adverse event reports. You may be looking at published literature reports of adverse events. So, you are really looking at all the available information on safety to bring into the equation. Dr. Robert Meyer will be talking about the clinical parts of what we are looking for in the safety evaluation of your product.

Now, there is a whole roster or battery of studies that are possible to be conducted to look at the safety of a product. There are the in vitro tests or the animal tests. There are numerous types of clinical testing that can be requested. And, there is really no one recipe that you can follow for any given product because every product is unique and one of the challenges of our jobs is that we have to look at every application and every product and decide what, from that smorgasbord of possible studies, we need to evaluate your product and decide that it is safe for its intended use.

So, it is not a recipe that you can

follow. Even though there is a large list of possible studies you can't just consider it to be a recipe. It is more of a buffet or a smorgasbord and that is why there has to be a lot of interaction between you, the sponsor and we, the FDA on evaluating your situation and deciding what is needed.

Now, Bob Temple made a comment before the break about a long marketing history that doesn't tell us a whole lot about the product with regard to effectiveness. That is very true, as I think he tried to point out. He also "caveated" that a long marketing history can provide some information about safety but it can't provide all the information we may need in evaluating your product.

Particularly for unapproved marketed products, there is no adverse event reporting system in place really so that we don't even have that part of the data equation as we are evaluating these. So, you may be able to rely on a long marketing history to exclude catastrophic adverse events from the active moiety, but it is very hard to rely on that for

slid data on common adverse events and less serious adverse events.

It is important to remember that demonstration of safety is required for all the applications. Dr. Temple had on his slide that in some cases you might not need to demonstrate the effectiveness because there are some areas where that had already been established or you could reference someone else. But for drug safety, if you get to the NDA stage, we are going to be looking at every application to have demonstrated adequately the safety of the product. Of course, there are various places where those data can come from.

In the end, our approval decisions are judgments that we have to make on the benefit/risk ratio of your product. So, we have to look at what are the benefits of your product; what condition you are treating; how effective is the product; what are the alternatives to the product. Then we have to look at the safety profile. And, there is no one benefit/risk equation that meets all

products. Obviously, we expect products that are used for more minor, self-limiting conditions to have a very good safety profile while we accept a more severe set of potential consequences for a drug when it is treating something much more serious. For example, we would never tolerate for an antihistamine the types of toxicity we tolerate for cancer chemotherapeutics. So, it is always a benefit/risk assessment. There is no standard equation that you can look to for figuring out whether your benefit/risk assessment passes the mark or not because in many ways it comes down to judgment.

But, again, highlighting the need to have that dialogue with my divisions early on so that they can help you decide where to look for the data you might need to support the safety of your application and in places where you need to do additional studies, help you make the best use of your time and money by making sure that you do the right studies, and you do them correctly so that you don't bring them in later with your NDA only to

be told, well, yes, you did the Ames test but you didn't do it right so, please, go do it again.

So, if you do find yourself in the green boxes, you really need to work with us, to come in and look for advice, and the best way is, as Kim Colangelo pointed out on her slides, to get in contact with the supervisory project manager for the division where your product will be reviewed and request a meeting.

With that, I am going to stop with the high overview comments and turn to Dr. David Jacobson-Kram to talk about the preclinical requirements. I will tell you, as David is coming up here, that he is our resident expert in clip art so you can expect some interesting slides.

DR. JACOBSON-KRAM: Thanks, John. Good afternoon. I am going to spend probably about the next ten minutes talking about preclinical safety testing and how that relates to products that have been potentially on the market for a long time but are still unapproved.

Here you have a list of examples of

preclinical and nonclinical studies that are often requested for a new molecular entity. Often pharmacology studies are done very early on as part of proof of concept. These are mechanistic. Some of them are done in animal models and are done as part of discovery, and these are not usually GLP compliant.

After that stage there is a whole series of safety tests that are required for an NME. These are done under Good Laboratory Practices, and some of these studies are submitted with the IND and some are submitted with the NDA. The examples that I show here are safety; pharmacology; general toxicology; genetic toxicology; pharmacokinetics; ADME studies which look at absorption, distribution, metabolism and excretion of the drug; reproductive studies; carcinogenicity studies; and a kind of the catch-all category, for example if your drug is used for a pediatric indication you will likely be asked to do juvenile studies.

Well, why do we ask for these studies? We ask for them to determine - and, remember, this is

in the context of an NME - whether it is safe to put the drug into humans for the first time. Many of you know that phase 1 trials are often done in healthy volunteers so there is no risk/benefit equation at that point in drug development. So, we insist that the conditions of these trials are extremely safe.

We determine what constitutes an initial safe starting dose in the clinical trials. These studies help determine what a safe stopping dose would be in clinical trials. Perhaps most importantly, it identifies dose-limiting toxicities, in other words, what organs or systems are at risk and what should be specifically monitored during the clinical trials. But perhaps most relevant for this audience is that these studies also assess potential toxicities that can't be identified in clinical trials.

So, waivers for toxicology studies, for unapproved drugs that have been widely marketed, and here I am saying for significant periods of time and in significant quantities, certain of

these tests could be waived. For example, single and repeat dose toxicology studies designed to evaluate acute and chronic effects can be waived because there is a long clinical experience so we know what the general toxicity effects are. This would include general toxicology and safety pharmacology studies. This is potentially a big savings for sponsors because chronic studies are done generally in two species and, because the drugs are given for many, many months, those can be quite expensive studies. However, some toxicities cannot be readily identified from clinical experience, and the need for studies to evaluate these toxicities will be done on a case-by-case basis.

So, what toxicities cannot be easily identified by clinical experience? One is genetic damage. If you ask the question does this drug have the potential to cause mutations in DNA or changes in chromosomes, this is generally not assessed in a clinical trial.

Effects on fertility, this is very hard to

detect. There is a high background of infertility and trying to tie an epidemiological cause to effects on fertility is extremely difficult.

Teratogenicity or birth defects - you probably know there is a high background rate of birth defects in the population. However, potent teratogens would be detectable epidemiologically because the time between exposure and seeing the adverse event is relatively short so that makes tying the exposure and the effect together less difficult.

Carcinogenicity studies are really difficult. There is a high background in the population. There is a very long latency period that would make epidemiological studies very insensitive, especially for common cancers. For example, if a drug caused an unusual kind of cancer, like diethyl stilbesterol did, that connection can be made. Although it wasn't made real quickly, it ultimately was made. But let's say a drug increased your risk by some percentage for a common cancer with a very long latency

period, making that connection between the exposure and the disease would be exceedingly difficult.

So, data that address these toxicities may be available in the open literature so if the studies had been done and they are available to us, they don't need to be repeated. However, the need for these studies to address these potential toxicities will always be done on a case-by-case basis.

Perhaps the one that sponsors find the most onerous because of expense and time are carcinogenicity studies. The need for carcinogenicity studies is governed by several criteria. If the drug is indicated for continuous use, for six months or more, or is used frequently in an intermittent fashion for chronic or recurrent conditions, such as allergic rhinitis, anxiety or depression, typically we would require data from carcinogenicity studies.

Or, if there were a specific concern about that drug, for example, if it was positive in genotoxicity assays, if we had data that suggested

that it caused genetic damage, chemicals and drugs that do that have a high probability of being carcinogens, we would likely require carcinogenicity testing.

If there were information from a product class, for example, if we had data from a class of drugs all of which had a certain kind of carcinogenicity associated with them, again, we would ask for carcinogenicity studies.

If there were a signal from structure activity relationships, there are computer programs now that are actually quite sophisticated so you can enter the molecular structure of your drug into the program and then, based on a historical database, the program will then tell you with some probability what is the chance that your drug will turn out to be carcinogenic. It will also tell you kind of the confidence level that it has in its prediction.

Also, if there were evidence from repeat-dose studies of a shorter term nature, for example, if you did a three-month study and you

were already seeing hyperplasia in certain organs, this would be a red flag to suggest that if you continued exposure those hyperplastic changes would ultimately turn into tumors.

What if carcinogenicity studies are positive? Is that the end of the story? Well, it is not because there are an awful lot of drugs in the PDR that have positive carcinogenicity data associated with them. So, some of the things that you would ask yourself about if you did get a positive result is what is the drug indication? Again, as John pointed out just a few minutes ago, we are much more tolerant of adverse effects for drugs that treat life-threatening conditions for which there are no other alternatives than for ones that are relatively mild.

We would ask who is the target population? Is it a geriatric population, pediatric population, obstetric population? Obviously, the risk/benefit changes enormously depending on the indication and the population. What is the likely duration of use? We know that the longer you are

exposed to a carcinogen the greater your risk of ultimately developing cancer.

Are there other drugs already serving this medical need and what is their safety profile? So, if your drug turns out to be carcinogenic at exposures that are comparable to what is going to be used clinically and there is another drug out there that is equally effective that doesn't have a signal for carcinogenicity, that is probably not good news.

What is the margin of exposure? What is the safety factor here? So, what are the exposures in the animals that get tumors compared to the exposure levels in the patient population which is getting the drug clinically? Obviously, the bigger the margin of exposure, the more comfortable we feel about the risk. Carcinogenicity generally is not an approvability issue. More often than not it ends up being a labeling issue.

I will be happy to address any questions when we get to the question and answer part of the presentation. Thanks.

DR. MEYER: Good afternoon. Again, I am Dr. Robert Meyer and, just to be clear, Director of the Office of Drug Evaluation II. It occurred to me that we probably should have at some point this afternoon had an organization chart for the Office of New Drugs but my particular office has a division that does pulmonary and allergy drugs, plus a division that does metabolic and endocrine, and then a division that does analgesics and rheumatologic drug products.

Talking about some of the clinical considerations in demonstrating drug safety for the purposes of an NDA, I think I will start off by just saying that there is obviously, in what we are talking about here today, a spectrum of what would need to be demonstrated. On the one hand, we have the 505(b)(1) application where there is a need for a full demonstration of all aspects of safety, both preclinical and clinical, all the way over to, in essence, a generic drug or a 505(j) where the demonstration of safety and efficacy is done through showing that you are pharmaceutically

bioequivalent to the reference product. If you are a (j), then we assume that you will have the same efficacy and safety that has already been shown. A lot of what the unapproved drugs would face coming into us with some areas that have been defined and some areas that are left uncertain.

In terms of the FD&C Act itself, the standard for safety is that, as Dr. Jenkins earlier said, the drug is safe for its labeled indication. The Act actually calls for all tests that are reasonably applicable to be done. I don't have a laundry list because that is going to be quite varied depending on the circumstances, but often will include physical examinations, chemistry examinations, laboratory hematology examinations, ECGs or cardiograms, but may in special circumstances include things as elaborate as CT scans or very specialized tests. So, it really depends on the drug in question and the indication in question as to what might be expected.

But an important point about safety as opposed to efficacy is that the standard for

efficacy is that we have randomized, controlled trials that show a statistical finding that the drug is effective. Generally those findings are replicated in at least two trials. For safety we seldom have hypothesis testing. What we expect in an NDA is a demonstration that the drug has been adequately examined and that we do not find safety issues that would preclude its use for its labeled indication. But, with some exceptions, there are no trials that generally have a safety hypothesis where you get to the end and you say, ah, they met their statistical expectations and, therefore, they are safe enough for approval. So, there is some judgment to it. I guess that is an important point.

The other point I was going to make is that, besides there not being a single statistical test or series of statistical tests for safety, is that there is uncertainty. Even when you get to the NDA approval stage there is uncertainty and the level of uncertainty that we are going to tolerate really is dependent on the drug. The level of

uncertainty about the safety, in other words how much you know or you don't know about the drug - you tolerate much more for a drug that might be having a life-saving indication than for a drug that might be chronically used for a more trivial or symptomatic condition.

So, all that being said up front, this is sort of a slide that really would pertain to a 505(b)(1) or a full application. For a new molecular entity, something that the FDA has not previously seen, we would expect enough adequate safety data, both controlled and uncontrolled, to allow for a risk/benefit determination. And, there are guidances that talk to that. There is an ICH guidance that has a companion FDA guidance that asks for a minimum of the following for chronic use drugs for non-life-threatening conditions: 1500 total patients exposed; with data from at least 300 patients for 6 months and 100 patients for 12 months.

The ICH guidance and the FDA guidances do clearly state that the extent needed might vary

and, in fact, could be higher than these numbers depending on the circumstances. These circumstances are described in various places but one place I would refer you to is the *Pre-Marketing Risk Evaluation Guidance* which is cited on the slide.

As I previously said, I think we are really talking about a spectrum or world here where we are living somewhere in between this expectation of the full new molecular entity or (b)(1) application, the other extreme being the (j) application or the abbreviated new drug application where what you are doing is demonstrating bioequivalence to an already approved product and getting the same labeling. Probably much what we are talking about here for unapproved drugs coming in would like somewhere in the middle or somewhere in that spectrum.

So, the beginning question that one would need to pose for an unapproved drug seeking approval, and one that my division and other divisions with the Office of New Drugs would pose,

is what is already known and proven for that drug? So, has the drug moiety itself ever been approved? By moiety, that really focuses on the specific drug itself and things like salts and esters are sort of under that umbrella. So, has the drug ever been approved either through the NDA process or has it been included in the final monograph, or was it addressed in the DESI review? Of course, the DESI review had more to do with efficacy but, nonetheless since we are talking about the risk/benefit ratio, safety is informed by the efficacy. Has it been approved for any indication? If it has been approved for any indication, is it is a similar or the same indication?

If the answer to this is yes, there might not be as much need for the demonstration of safety for such a product to be approved. If the answer is no, there is still a possibility that there is information that would be quite useful to the sponsor and to the FDA in making a determination about the relative safety of that drug. So, there could be literature from foreign marketing, for

instance, or from randomized, controlled trials or case series. Probably the least helpful, although it does make the literature, are anecdotal reports of drug use.

Now, if the drug product was previously approved for the same or similar indication and when I use similar you could point to many examples of this but, say, if a topical drug had been approved at some point for pruritus and now was seeking an indication for something like urticaria there are some similarities to that kind of use. The previous findings of safety may be informative and then there would be a possibility of not needing much additional safety data. Or, if there was a need for additional clinical safety data, it might be quite a bit less than if you were talking about a de novo approval.

If the drug substance was not previously approved or if the approval was for quite an unrelated indication there still, as I said in the previous slide, might be literature or other information that could decrease the amount of

safety data needed.

I would say that one very rich source of safety data for us would be if efficacy trials are needed for the approval of a now unapproved drug. That is a very good source of safety data because it is coming from randomized, controlled trials where we actually have a comparator group to help define the safety findings, or help us to interpret the safety findings. The ascertainment of the safety data would be quite good in such trials. So, the good news is if you do need to do efficacy trials that will provide a lot of safety information as well.

One thing I wanted to be clear on and, unfortunately, this slide has one word that I will point out, but Bob Temple spoke to this. I spoke to it a little bit previously. The advice that I am giving here is really about the active moiety. The drug moiety, from our standpoint, is not made different by salts, esters and dosage forms. The drug product is made different by those and, therefore, it has ramifications for the application

route, as Ms. Colangelo pointed out earlier. But from a scientific safety standpoint we really look much more at the moiety.

So, information from the same active moiety from other manufacturers, from other salts, esters or dosage forms may provide relevant safety information that will be useful to the sponsor and useful to the FDA in assessing the safety of a product that is coming in for review under an NDA.

Of course, one of the things in terms of how useful that prior data is, really, how does it relate? Is it the same route of administration? For instance, corticosteroids can be given in many, many different routes of administration. We have seen inhalation corticosteroids that have been previously approved in ophthalmic drops or in terms of skin creams or suspensions. While you get some useful information if, for instance, you are taking the example of a corticosteroid for inhalation, if that was given orally in the past and you know there is systemic absorption with the inhalation route the previous finding of safety by the oral

route would inform a lot of the concern about any systemic toxicity of the corticosteroid by the inhalation route. But we would still have a lot of questions about the local safety. In fact, we would probably have questions about just how much the difference in the pharmacokinetics to the systemic route of administration would affect the systemic safety as well. But, nonetheless, there would be a fair amount of data that would inform from the oral route to the inhaled route.

Is the drug given for the same duration or the same population? Duration of use is a very important issue. There are some drugs like antihistamines that might be given for a very short period of time or might be intended for much longer duration of use. For instance, if it is for seasonal allergic rhinitis it might be very short. If it is for perennial conditions it might be quite a bit longer in duration. Obviously, if you are proposing a longer duration and the approval is for a short duration, then some questions will be answered but chronic use questions might still

persist.

Similarly for the population considerations, we have some populations that would be particularly considered vulnerable. We are going to hear more about pediatrics in a bit. But changes in population may change the risk/benefit ratio and might change the amount of data needed.

What about the exposure of the proposed product compared to the approved product? Does the PK show similar overall exposures, in other words, the area under the curve for exposure or even for the C-max, the maximal amount of drug that the body sees? Is that more? If it is more, then we would probably have some safety questions that couldn't be answered by referring to the safety data from the previous drug. If it is less, then a lot would probably be covered by what we know from the drug as it was previously approved.

So, all these questions and considerations will really factor into what we consider to be "known." I put that in quotation marks because from the FDA's standpoint we are a little bit like

Missourians. We are in the "show me" mode. This is not “sort of known” in a kind of a generic public sense, but what is tangible to us; what are we able to say we, in fact, know about this drug's safety and what is unknown for that proposed indication? It is really the unknowns that need to be addressed through the studies and the application for the drug to be approved. That is particularly true in a 505(b)(2) where, in fact, what you need to demonstrate is that the differences between you and your reference product do not lead to safety issues of such concern that they would impact on the approvability of the product.

This point has been made previously. I was about to say I don't want to belabor it but I think it is a point worth belaboring, and that is that long-term marketing use without prior approval and without available, useful data in the literature really does not provide much evidence of safety. It certainly speaks to there not being gross problems but actually a lot of even some

approved drugs, with very careful, longer-term studies, have shown new findings that we hadn't expected. So, clearly, for drugs that have not been through the approval process and really have not been through any kind of rigorous evaluation the unknowns are much, much greater and, therefore, the safety concerns are much more real.

The reason that I say that the existence of long-term marketing without other information is not useful to us is that, as Dr. Jenkins mentioned, there is not really a defined adverse event drug system outside of the requirement, since 1984, that for unapproved drugs serious ADEs are reported. But we don't get annual reports. We don't get reports that are not serious. So, we really don't have a good, reliable source to look at the post-marketing experience.

Furthermore, there is often a lack of preclinical characterization. David talked about that earlier. But without animal characterization we may not know clinically what we are even looking for with some of these products, particularly if

the drug moiety in question is really not related to or has not been previously approved.

To summarize my section, and again I am going to be serving on the panel so I am happy to take more questions, particularly questions about more specific circumstances because I want to give a fairly high level talk here. But in summary, for an application for an unapproved drug to get approved, FDA needs assurance of the safety to make the risk and benefit decision. That risk decision is informed by previous findings from products with that drug substance and/or literature but, to the degree that those do not answer the questions and unknowns are left, then the application needs to specifically address that with new data.

Again, from the FD&C standpoint, the specific testing that would be required in clinical tests varies quite a bit so the bottom line is that these are discussions worth having with the individual Drug Review divisions as to what kind of findings would be needed, or what kind of studies would be needed to support an application for a

drug coming in to the approval system. Again as I said previously, fortunately, a very rich source of safety data would be if efficacy trials are needed because they will get good control data out of that, not perhaps all the data we would need but certainly good data to help inform the decision. With that, I think I will end. Thanks.

MS. AUTOR: Thank you, Dr. Meyer. Our next speaker is Lisa Mathis. Dr. Mathis is an Associate Director in the Office of New Drugs and head of the Pediatrics and Maternal Health Staff. That staff functions to consult on pediatric, pregnancy and lactation issues and clinical protocol study reports and labeling. Dr. Mathis is a Board Certified practicing pediatrician who joined the FDA as a medical reviewer in 2000, and she is going to talk about the Pediatric Research Equity Act and pediatric considerations.

**Pediatric Research Equity Act:**

**Pediatric Considerations**

DR. MATHIS: Good afternoon. I am going to be talking today about the pediatric legislation

that was passed that requires or encourages pediatric studies of new and marketed drugs.

The first program is the voluntary program of the Best Pharmaceuticals for Children Act, also known as BPCA. This basically renewed the pediatric exclusivity incentives from FDAMA. The mandatory program is the Pediatric Research Equity Act which was signed into law in 2003 and restored some of the important aspects from the pediatric rule.

The Best Pharmaceuticals for Children Act is a program that allows the sponsor to submit a proposed pediatric study request, or a PPSR, that outlines the proposed study and the public health benefit of conducting such research in the pediatric population. The FDA then may, in response, issue a written request which is basically an outline of studies needed in the pediatric population. So, the PPSR is, in essence, a request for a request. If the studies are performed per the written request, then six months of exclusivity will attach to the entire moiety.

Now that you are used to using little boxes and arrows from today, this is the process of industry submitting the PPSR and then the FDA reviewing that PPSR and issuing a written request. If industry declines the written request, they have to notify us and if they don't respond to us in 180 days we could refer that written request to the NIH. That probably won't have a lot of bearing on you all and the studies that you will be doing.

Pediatric exclusivity resulting from this program is a six-month period that attaches to existing patent or exclusivity. It is not a stand-alone exclusivity. There is a guidance on the web, Qualifying for Pediatric Exclusivity. This guidance was actually written for exclusivity as it existed under FDAMA so there are some differences but not that many. It is actually very helpful.

Now for the Pediatric Research Equity Act, the Pediatric Research Equity Act is triggered when there is a new ingredient, new indication, new dosage form, new dosing regimen or new route of

administration. I am sure as you are looking at this list you can see that it is probably going to apply to many of the products that you are thinking about bringing in as NDAs.

A waiver or a deferral may be granted. I actually have the slides on specifics about waivers and deferrals as backup so I am going to jump up to them because I think that that will probably be really helpful for you now. So, a waiver is granted if the studies are impossible or highly impractical; there is strong evidence that the drug or biologic would be ineffective or unsafe in the pediatric population; or if the product does not represent a meaningful therapeutic benefit over existing therapies and it is not likely to be used in a substantial number of pediatric patients. Don't forget that "and" in this last bullet.

For a partial waiver it is all the same conditions that there are for a full waiver, only it is for a subset of the pediatric population by age. There is also an additional bullet that gets added here, and that is if you have a product that

you can't make into a suitable formulation for a specific subsection, say, neonates or kids younger than six who can't swallow pills, then that would be grounds for a partial waiver in that younger age group as well.

The deferrals come if the drug or biologic is ready for approval in the adult population so we would never hold up approval of the adult indication, or if additional safety and effectiveness data is needed and the rest of the product is ready to be approved, or if there is another appropriate reason that you come in and talk to us about.

There is a guidance on the web that is specifically for PREA. The pediatric assessment must contain data adequate to assess the safety and effectiveness of the drug or biological product, and information on the dosing and administration in each of the pediatric subpopulations that it is approved for.

This is a little chart of BPCA versus PREA. Under BPCA the studies are voluntary and if

you have an orphan product it could qualify for exclusivity. Under PREA the studies are required and orphan drugs are exempt.

PREA is for biologics and drugs both, while BPCA is for drugs only. And most importantly, they both sunset on October 1, 2007. So, the information that I am telling you now holds true up until October and then after that we are not sure what will be coming along.

There are two pieces of pediatric specific legislation, and it is important for you to know, when you are submitting your applications, these requirements and incentive programs. And, while they do not apply to all drugs, make sure that any obligations and opportunities have been discussed with the review division before you submit your application, or at least in the process of submitting your application. That is it.

MS. AUTOR: Our next speaker is Kim Dettelbach, from FDA's Office of General Counsel. Kim is going to speak about patent and non-patent exclusivities. Ms. Dettelbach is an Associate

Chief Counsel in the Food and Drug Division of the HHS Office of General Counsel. Her practice concentrates on issues relating to generic drugs and exclusivity, 505(b)(2) NDAs, orphan drugs and pediatric development. She has been with FDA for eight years.

**Patent and Non-Patent Exclusivities**

MS. DETTELBACH: Good afternoon. My name is Kim Dettelbach and, as Deb said, I am an attorney in the HHS Office of General Counsel in the Food and Drug Division.

My talk today is entitled patent and non-patent exclusivities. Fortunately for me, I am late in the day and much of what I have to say has already been covered by Gary Buehler and others. So, fortunately for you, I should be mercifully brief.

I am going to discuss some of the intellectual property considerations for applicants and protections for NDA holders and the circumstances in which they are available. I will begin by briefly discussing patents and the way in

which patent protection is required by statute to be taken into consideration in the drug approval process. Again, this was covered by Gary and Kim Colangelo so we are going to breeze through those slides. I will then discuss statutory non-patent exclusivities and the circumstances under which these non-patent intellectual property protections prevent FDA from accepting or approving certain other applications.

I note at the outset that all of the protections that I will discuss are created by statute. FDA doesn't have discretion to create additional periods of exclusivity where a drug is particularly important or where it has been particularly different to develop. The de facto exclusivity that Deb Autor was talking about is a separate matter and I will not be discussing that today.

As Gary and others told you, in addition to all the scientific requirements that folks have talked about today, when you submit an NDA under section 505(b)(1)(g) and 505(c)(2) of the Federal

Food, Drug and Cosmetic Act a sponsor is required to file with FDA and FDA is required to publish in that "Orange Book" patents that claim approved drug substances, those are active ingredient patents; drug products which tend to be composition and formulation patents; or approved methods of use.

Sections 505(b)(2) and 505(j) of the Act require that ANDA and 505(b)(2) applicants certify to those patents that are listed. Certain patents are not listed, for example manufacturing process patents. Those can be protected outside the drug approval process through the normal channels. But the patents that are required to be listed have implications for when FDA can approve competing applications.

ANDA applicants and 505(b)(2)s referencing approved drugs must include certifications to the listed drugs for the drugs they reference. Gary went through those I think in some detail so I won't. But, as Gary noted, the paragraph III and the paragraph IV certifications are the ones that tend to delay approval. Paragraph III says that

you are willing to wait until the patent expires before you are going to seek a final approval and paragraph IV says that you are challenging a patent as unenforceable or invalid or not infringed.

When you have a paragraph IV certification, that may delay your application from being approved. You are required to notify the sponsor of the NDA and they have 45 days in which to sue you upon receipt of that notice. If they sue you within those 45 days for patent infringement, there is a 30-month stay that prevents our approving your application until the expiration of 30 months or until you have won your patent lawsuit.

In addition to the protections derived from patents, the Federal Food, Drug and Cosmetic Act also provides for certain protections known as marketing exclusivities. These protections tend to take the form of bars on either our acceptance or approval of applications and they are different, as I noted before, from the de facto exclusivity referred to in the CPG. De facto exclusivity

refers to actual time on the market without approved or unapproved competitors. The statutory exclusivities are bars on our approval or acceptance of competing applications.

There are four types of statutory exclusivity that I will discuss today. Gary also discussed 180-day exclusivity which is available to the first generic applicant to challenge a listed patent. I will not be discussing that today. The four exclusivities that I will be discussing are five-year new chemical entity exclusivity, three-year new clinical studies exclusivity, seven-year orphan drug exclusivity, and six-month pediatric exclusivity. Again, Lisa Mathis discussed pediatric exclusivity in some detail so I will keep that discussion pretty short.

Five-year new chemical entity exclusivity-Byou will find that the word "exclusivity" actually doesn't appear in the Federal Food, Drug and Cosmetic Act except in the 180-day exclusivity section and that is a recent change. So, if you are looking for it under the

word "exclusivity" you won't find it. But the descriptions are in sections 505(c)(3)(D)(2) and (j)(5)(D)(ii) of the Federal Food, Drug and Cosmetic Act and in regulations at 21 CFR 314.108. Five-year exclusivity is granted to a drug that contains no active moiety that has been approved by FDA under section 505(b). That applies only to active moieties that have not been approved either alone or in combination. So, if your moiety has been approved in combination with another moiety and you are seeking approval for a single ingredient product it will not be eligible for five-year exclusivity.

An active moiety is defined as the molecule or ion responsible for the physiological or pharmacological action of the drug substance. As others have pointed out, that includes salts and esters.

Five-year exclusivity runs from the time of NDA approval and it bars FDA from accepting, not from approving but from accepting for review any ANDA or 505(b)(2) application for a drug containing

the same active moiety, for five years if the ANDA or 505(b)(2) doesn't contain a paragraph IV certification or, if you are challenging a listed patent with a paragraph IV certification, you can do that at four years.

The second kind of exclusivity that is available if your moiety has been previously approved either alone or in combination is three-year new clinical study exclusivity. The description of that can be found in sections 505(c)(iii)(D)(iii) and (iv) and 505(j)(5)(D)(iii) and (iv) of the Federal Food, Drug and Cosmetic Act and in our regulations at 314.108. It is granted to an application or supplement when it contains reports of new clinical investigations other than bioavailability studies. So, bioavailability studies are not eligible for three-year exclusivity and they must be conducted or sponsored by the applicant and essential for approval.

Now, we have had situations where someone has conducted a study that gives us an answer that we already know because they want to get three-year

exclusivity, for example, for an OTC switch where we already knew that the drug was safe for OTC use. In that case, those studies are not deemed essential for approval and are not eligible for three-year exclusivity.

Three-year exclusivity runs from the time of NDA approval and it bars FDA from approvingB-remember, five years was from accepting and this is from approving for a three-year period any ANDA or 505(b)(2) application that seeks approval for the same conditions of use of the drug for which information was submitted and exclusivity was granted. So, you get exclusivity for the studies you do. One way to think about what is blocked is that if the same studies that supported the exclusivity could also support approval of your drug, then it will be blocked by that three-year exclusivity.

The next exclusivity that I want to talk about is orphan drug exclusivity. That is discussed in sections 526 and 527 of the Federal Food, Drug and Cosmetic Act and in CFR at section

316 and the following sections. There are two steps to getting orphan exclusivity. You must first be designated as an orphan drug, and that is very important because if you submit your application before you receive your orphan designation then it will not be eligible for orphan exclusivity. So, first you need to go through the designation step then through the approval step. Orphan Exclusivity is granted to drugs designated and approved to treat diseases that affect fewer than 200,000 people in the United States or, if they affect more than 200,000, you can make an argument that you couldn't recover your costs of developing the drug.

This also runs from the time of approval of an NDA or a BLA. So, this is the only one that affects BLAs of the ones I have discussed. It bars FDA from approving any other application, including ANDAs, 505(b)(2)s and 505(b)(1)s or BLAs for the same drug for the same indication. So, the protection is in some ways broader because it blocks more things but it is only for the drug for

the indication.

Whether a subsequent application is for the same drug depends on both the clinical and the chemical characteristics of the drug. Chemically, that may be more self-explanatory. Clinically, a drug is considered a different drug if it is safer, more effective or it is what we call a major contribution to patient care. That is a pretty hard standard to meet but it is when the drug is developed in such a way that it is much easier to take. For example, I believe we once found a major contribution to patient care where there was an injectable that I think you had to give twice a day and someone developed a once a month so you went from two injections a day to once a month. That was considered a major contribution to patient care and a different drug as a result.

Lisa talked in some detail about pediatric exclusivity. As she noted, it is in section 505A of the Federal Food, Drug and Cosmetic Act. There are no regulations but there is the guidance from September, 1999 which is quite helpful and it is,

as she said, open to reauthorization this year.

Pediatric exclusivity grants an additional six months of protection at the end of listed patents or exclusivity for all the sponsor's products containing the active moiety when the sponsor has conducted and submitted pediatric studies in response to a written request. And, again, this is very key. If you want to apply for pediatric exclusivity you must first get a written request and submit the studies only after you have received that written request. Studies that are in-house before the written request is received by you or is written by FDA don't qualify for pediatric exclusivity. So, it is important that you do these steps in order.

One more word about pediatric exclusivity, it takes on the characteristics of whatever exclusivity or patent it attaches to. It is not a patent extension but to the extent a patent blocks FDA from approving a subsequent drug, for example, because someone has a paragraph III certification and is willing to wait until that patent expires,

the pediatric exclusivity will add six months to the end of that patent. To the extent pediatric exclusivity attaches to five-year exclusivity, it will block our acceptance of an application for five years and six months, or four years and six months if you have a paragraph IV certification, and three-year exclusivity is also extended and orphan exclusivity in the same fashion to add an additional six months and to take on the character of whatever exclusivity you are extending. That is all I have for today. I am happy to answer questions later on.

MS. AUTOR: Thank you, Kim. Well, I am hoping that after our safety and efficacy discussion and making you all feel pretty low, Kim's discussion of exclusivity helped a little bit. Mike Jones is going to touch on user fees and waivers and then maybe Sally Loewke will talk about the role of the unapproved drugs coordinator.

Mike Jones is our next speaker and Mike is a pharmacist who has been at FDA for 17 years and with the user fee program since 1993. He is a

special assistant in the Office of Regulatory Policy.

**User Fees and Waivers**

MR. JONES: Thanks, Deb. Congratulations for making it so far in the workshop. I guess I have 15 minutes to let you know everything that I know about user fees. Once that is done I think I can retire!

Well, in essence, we have three types of fees. We have application fees and that is generally a one-time affair. Then, once your product is approved we have the annual product and establishment fees so you get invoiced for that every year. Along with the application fees, once that is approved and, say, you want a new indication you may be eligible for a fee at that time. So, in essence, we have three types of fees. Most of my remarks will be about the application fees.

Just to let you know, the fees this year for an NDA that requires clinical data for approval are close to $900,000. A supplement without

clinical data is about $448,000 as well. So, those are the type of fees. I also kind of put on there INDs. We talked about INDs several times earlier and I get questions all the time, well, gee, I have an IND. Do I have to pay for that? Well, no. That is one of the things that you don't have to pay for. At the bottom I have that a supplement that doesn't require clinical data for approval doesn't pay a fee as well. For example, maybe you have a chemistry, manufacturing and control supplement. We wouldn't expect normally a fee for those.

Collection of feesB-well, some folks believe that we are going to send you an invoice. Well, that is not our procedure. Basically what you are supposed to do, you are supposed to pay your fee to the Mellon Bank in Pittsburgh at the time of your application submission. Now, notice that when Kim talked earlier about what you include in your NDA, don't include your check in your NDA. Then you would get a call from me, you have good news and bad news. The good news is, yes, FDA has

your check. The bad news is I got your check. We will be sending that back to you and you will have to start that process over again. So, again, send that off to the Mellon Bank.

Just a point of reference for product and establishment fees, we will send you an invoice for those. Generally, we pre-bill and we send you those bills in August before our fiscal year starts. Our fiscal year starts on October 1. Then what happens is that since we pre-bill we don't know what is going to be approved during the year and we will send you an invoice after the fiscal year for new approvals during that fiscal year.

I want you to be aware of the bundling policy and definition of clinical data. When it comes down to the point where you figure that you are going to have to submit an NDA you are going to want to know, especially if you have multiple dosage forms like if I have a capsule and a tablet that is the same moiety, can I put those in the same NDA? Well, the answer is no. But here we tell you why. I mean, basically a different dosage

form needs its' own application.

Also, we have been talking about clinical data for a good portion of the day. With user fees there are always two definitions. There is the normal definition which everybody would think and then there is the user fee definition. We have our own user fee definition for clinical data. You noticed earlier I think that Kim talked about clinical data not being bioavailability data so that is kind of carved out as well with clinical data. This is on our website. I have an address for our PDUFA website later on in the slides.

I kind of told you that we have two definitions for everything for user fees. Here is another one of those things. You would think, well, gee, I have a human drug application. I will give it to a human; it is a human drug application. Not so. Basically, what the statute says is that 505(b)(1) applications are human drug applications. The statute also kind of says that 505(b)(2) applications that are for a new entity or a new indication for a use, which is broadly interpreted,

are human drug applications. Gary, sorry, generic drug applications are not human drug applications! So, basically 505(J)s have been carved out. It is not explicit in the statute, but it basically says (b)(1)s, (b)(2)s. Just for completeness, there are certain biologic applications that are also considered human drug applications.

Kim did a great job earlier in telling the difference between (b)(1) and (b)(2). I just want to reiterate a little bit that for a (b)(1) in essence you own the data or you have the right of reference. For a (b)(2) you do not own or you do not have the right of reference. So, those are key parts of what the (b)(1) and (b)(2) are.

What is a fee paying 505(b)(2)? I kind of alluded earlier to that phrase new indication for a use. Well, examples of those new indications for a useB-well, you can kind of see them. There is a new indication obviously; new patient population; new dosing regime; statements comparing to another product. If you kind of look at these examples, they are pretty similar to the PREA examples. If

you look at Kim's presentation, they are also very similar to the examples that you would get exclusivity for. So, if you are going for exclusivity, if you are going for PREA you can kind of expect that those (b)(2)s would be paying fees.

I also want to let you know that once we have a 505(b)(2) application that is approved, I mean, you can come in as a generic. As we already know, generics aren't human drug applications so you don't have to pay a fee for that.

I want to go over a few more exemptions with human drug applications. I think the first two examplesB-you know, if you get anything out of this talk, here is probably what you want to take home. If your drug product can be marketed under an OTC monograph or if your drug product can be under an ANDA, you don't have to pay fees. That may be the key point that you take home from today. How do I get my drug product to be under the OTC monograph or how do I get my drug product to come under an ANDA?

I also have in there the OTC monograph

drugs versus the NDA OTC drugs. I mean, if you submit an NDA for your OTC drug you can kind of expect that that is probably going to pay. OTC monographs, they don't pay. For INDs I already mentioned that we get questions from folks all the time. You know, I am going to submit my IND; how much money do I have to pay? For INDs you don't pay.

Drug master files. I have had questions from folks, you know, we want to submit a drug master file or we want to refer to a drug master file. How much do I pay? You don't pay. Just to let you know, I wanted to include our friends over in CBER. They also have carve-outs for applications and I just gave an example of a crude allergenic extract. That is not considered a product under a human drug application. We talked about certain 505(b)(2)s.

I also wanted to let you know about a couple of other exemptions. If you are a government entity, for example our friends at DOD, if they submit an application, and generally when

they submit their applications their products are only for distribution to the troops so those applications are exempt from fees. So, there are two things. You have to be a government application and it is not for commercial use. It has to hit both prongs.

We also have an orphan exemption. That orphan exemption is only for the application fee and your application has to be orphan only. So, if you have an application with multiple indications and one of the indications is an orphan and the other one isn't, you still pay. It has to be an orphan only. And, that is only for the application fee. You would still be eligible for product and establishment fees.

We have come to the point where, all right, I have to send in my NDA and I have to pay a fee. Is there a way for me to waive my fees? There are. These are the four major categories that we deal with and I will have a little bit to say about each one of them.

Hopefully, some of you folks will be able

to submit a waiver request for a small business. Basically, it has to be the first human drug application. It could be a (b)(1) or a (b)(2). Say, you are a big generic maker and all you have are ANDAs and this is your first (b)(1), then you would meet that eligibility. On top of that, we would need to know who you are and who your affiliates are. We will go through the Small Business Administration and they will make a determination whether your business is under 500 employees or not. What that gives you is a full waiver of that application fee. It is only one application so the second one that comes through the door, you know, you would be eligible for that application fee. You couldn't use that small business waiver more than once. So, you may want to plan ahead. Maybe you have one that could be a small business and one that can be an orphan. You would probably want to do your small business waiver before you do your orphan because if you submit that orphan, that is a human drug application and we will deny you on the small

business part. So, you know, plan and think ahead.

A lot of folks, what they do is when they submit their waivers, the public health and barrier to innovation, they send them both in for us to take a look at. In essence, your product is going to have to benefit the public or it is innovative. These are kind of fairly evident. I mean, if you are given a priority review, it is an NME, fast track. Those things have certain characteristics. You know, if it is a life-saving drug. That is pretty easy to show.

The other thing that we consider is treatment alternatives. If you are the tenth beta-blocker through the door you probably will not be able to show that you are benefiting the public health or that it is innovative. That is a higher hurdle to pass.

The other prong that goes along with these waivers. If you read through the waivers it says if it is necessary or because of limited resources. So, even though you could hit the first prong that it benefits the public health or it is innovative,

if you have the money to pay for this you should be paying for these things.

I want to fold this one in here. Generally this particular waiver is only used in cases where folks have had their applications here for many years. They don't really have very much regulatory business before us and they use it for product and establishment fees. It is called the fees exceed the cost waiver. We look at all the fees that you have paid versus all the costs that you have before the agency. The latest data we have is from 2005, and I think for an NME in 2005 our cost was about $2.5 million. So, if you have $2.5 million cost versus a $900,000 fee you are not going to win on that. The folks that usually get money back on this, these are the guys that basically were in existence before PDUFA and basically all they do is send in annual reports and what we do, we can waive their product and establishment fees.

We do have a fairly recent guidance document on this. It is on the website so I kind

of refer you to that. But I think that for most of you it is not going to be something that you are going to want to do. I don't think it is going to be worth it but I do have it here for completeness.

One of the disadvantages I guess with this particular waiver is that you need to pay this money up front and we won't know what the costs are until after the year ends so it could be two years before you see any money back from this. Those are typically questions that we get that folks are not real happy with.

Most of the stuff I have talked about so far is application fees. I did want to briefly talk about product and establishment fees. A lot of times I think what we do is we focus on the application fees but we don't consider what those fees are once we get those applications approved. In order for you to be assessed a fee for product and establishment, first the product needs to be subject to a human drug application. Again, if you are under a 505(j) you are not going to be eligible.

Gary, do you still have your "Orange Book?" It needs to be in the active portion of the "Orange Book." If it is in the discontinued portion, if it is no longer being manufactured or marketed, it doesn't pay a fee. Basically, you know, if it has like an AB rating, if it is the same as another drug product you don't have to pay a fee. Here is probably good news for some of you folks. If it is an OTC you don't pay the product and establishment fees. So, that might be a good thing for a lot of you folks.

I kind of alluded to this earlier. Another clause is that you have to have something pending after 9/1/92. I think we still have about five or ten applicants where they still haven't submitted a supplement since '92 and those folks are not eligible for product or establishment fees. I want to also let you know that the fee this year for a product is almost $50,000 and it would be for each different strength. So, if I had a 50 mg and 100 mg and a 200 mg I would have three product fees.

Establishment fees, a lot of times I get questions from folks saying, well, gee, I don't own the establishment. Do I have to pay the fee? Well, the answer is, well, yes. The question I ask him is do you own the application? And they say, well, yes, we do. Then I say, well, you get the responsibility for paying the fee. So, it is not the establishment owner; it is the application owner.

On top of that, for the product fees the applicant has to have had something pending since 9/1/92. The other question we get is we make the bulk drug substance, do we pay the fee? The answer is no. It is only the establishment that makes the product and final dosage form. That is the establishment that is responsible for the fee. You only pay an establishment fee if you pay a product fee. I get questions all the time, you know, when the inspector comes how much do I have to have my check written out for? Well, that is not the case. Basically what happens is in August and in November we send you a bill for these fees.

There is a possibility that you could share your establishment fee. You can see that for FY07 the fee is $313,000 but that could be split among various applicants. For example, if I own a facility and I am making 100 drugs for myself and then I contract out to Gary's drug company and I am making ten drugs for him and I am making five drugs for Deb and I making one drug for you, all at my facility, that $313,000 would be split four ways. It doesn't matter how many drugs are manufactured there; what matters is how many different applicants are there. Okay?

For the waiver process we expect a written request. I have my address on there. Most folks, what they do is they FedEx, DHL, whatever, they send these requests to me. I am going to refer you to only three pages in this old guidance document. It was FDA's interim guidance document for waivers on reductions in user fees. Basically those three pages request information that we would expect from everybody. For example, what is the name of your drug? What is your NDA number? Who is your point

of contact? That type of general information.

Once you kind of have that written up and you think you are ready to go, give me a call. There is usually something that happens that I can help you get that waiver request in better shape. This is our general office number. You can call in and I do return calls.

I wanted to give you the different websites. All the documentation that I have referred to in this talk is on our CDER website, also through the FDA PDUFA website just in case you need some more information there. That is it.

MS. AUTOR: Thank you, Mike. We were due to have a break after Mike's presentation but we are running ahead of schedule so, as long as nobody looks like they are asleep or needs to run out the door, I think what we are going to do is have Sally Loewke's presentation now and then we will follow that with a break and then a Q&A session after that.

I hope people will stick around for the Q&A because I think that will be useful and productive.

It is now my pleasure to introduce Dr. Sally Loewke. Dr. Loewke is Assistant Director for Guidance and Policy in the Office of New Drugs. In that position, Dr. Loewke works to ensure an efficient standardized review process by aiding in the development and implementation of review policies and procedures. As part of her duties, Dr. Loewke also serves as the unapproved drugs coordinator, which is what she is going to talk to you about today, and she has been with FDA since 1996.

**Role of the Unapproved Drugs Coordinator**

DR. LOEWKE: Good afternoon. I wanted to just give you a brief overview of basically how the coordinator position arose. It really came out of external inquiry about review standards and concerns about inconsistencies in the application of those review standards for marketed unapproved drugs. The position was officially established in December of 2005 by Dr. Galson, and the position was to be a point of contact for the Center and for OND.

Those organizational charts you heard about, here they are. I just wanted to show you an organizational chart for the Center for Drug Evaluation and Research under the leadership of Dr. Galson. I have highlighted a couple of the offices in which the coordinator would interact.

The duty of the coordinator at the Center level is really to be the point of contact to the external community, those interested in pursuing an application and who are not quite sure whether they are going, which path they are going to take, either the ANDA route, NDA, OTC. I would be the focal point. You can come, talk to me, and I would then either answer questions that I can or redirect you to the appropriate office. If you are looking for the (b)(2) application you would go to the Office of New Drugs. If you were looking to submit an ANDA, that would be in the Office of Generics, as you have already heard, under the Office of Pharmaceutical Science.

The User fee staff - I have referred many people to Mike; and I work with the Office of

Compliance as well. I am also a member of the compliance-led cross agency working group for unapproved drugs.

Here is another organizational chart. This is whittling down. This is the Office of New Drugs, led by Dr. Jenkins. I sit in the immediate office. We have six offices. You see the respective review divisions which they manage.

The coordinator's duties at the OND level are both internal and external. From an external standpoint, I would serve as a contact for you interested in pursuing an application within the Office of New Drugs. Generally I discuss the general approach to getting started. Many of you have called and you are not even sure how to get started so we talk about reviewing and summarizing literature if you are planning to submit a 505(b)(2) application. We go into a brief discussion of requesting a pre-IND meeting with the appropriate review division. I also have the contact information for those review divisions to make things a little quicker and easier for you.

From an internal perspective, I act as a liaison to the review divisions to aid in consistency in how we handle and respond to these requests. I interact with the divisions during the preparatory meetings for these pre-IND meetings; help facilitate responses and identify any policy issues that may arise. I try to attend as many of the industry meetings as my calendar will allow. I provide feedback and direction based on experiences I have with applications that have come in, and make sure that we are handling all of the applications in the most consistent manner possible. I update our divisions on related compliance actions as well.

So, what are my experiences from the industry perspective since I have been in this role? Well, as you can see, there have been multiple inquiries: Where do I start? Who do I submit to? The user fee question is very big in a lot of people's minds.

From another perspective, I also looked internally. What have I seen internally since I

started? A lot of people are unaware of the whole issue of unapproved marketed drugs so the goal really is to brief our people internally; to make them aware of the issues surrounding unapproved drugs, and the more aware we are the more attuned we are to these issues and can move forward to find solutions. I also will address any policy issues and, again, overall help standardize our approach.

Well, this workshop really came from you. It came out of the inquiries that I received as well as what the Office of Compliance received. We modeled our agenda really after the most frequently asked questions. As Deb had said earlier today, our intent was to give you a broad look at the application process and maybe some knowledge about the regulations that drive that process.

We are fully aware that you definitely must have specific questions about your drug product and, unfortunately, this isn't the venue to really be asking those questions, but I really encourage you to bring those questions forward to the individual review divisions when you come in

for your pre-IND meeting.

With that, again, how do you get started? If you are bringing in an application, a 505(b)(2) application, please review the guidances. You have been given many references today about guidances. These give you what our current thought process is and the most update advice we can give about the types of information we need. Please review the literature. Summarizing the literature and showing how it is relevant to your application is very important. Once you have done that legwork, it is really time to come in and request your pre-IND meeting.

Again, I think Kim offered you a website for contact information. You can also call me if you are unaware which review division you should be interacting with. The meeting package that you would prepare for that meeting-if you are relying on literature you really need to summarize that information and consider what is relevant to your application from the pharmacology/toxicology point of view, clinical pharmacology, clinical efficacy,

and clinical safety. It is important we know what your proposed indication is and your dosage form as well, and the CMC information that you may have.

In order for us to give you the best advice, it is important for you and for us to know what the full complement of data is that you have for your product. Knowing also the limitations of that data is very important because we need to figure out together how we are going to bridge that gap to get you moving forward. So, I ask that when you come in, really look very closely at what you have and what you don't have, and be very open because that will really end up with a very fruitful discussion.

I would really like to thank everybody who came here today. It was important for us to have this because we knew there was a lot of concern and unfamiliarity with the regulatory process. So, I really hope you found today's presentations very useful and, as you go home and you begin to digest some of this information and if you still find you have questions, please don't hesitate to call me.

If I can answer it, I will answer it. If I can't, I will find you the person who can. Thank you.

MS. AUTOR: Thank you, Sally. That is the last presentation of the day. Our plan now is to take a break for 15 minutes.

[Brief recess]

**Question and Answer Session**

MS. AUTOR: I think for the folks who have stuck it out this afternoon, this will be worth your while, I hope. I know it is a long day but I think perhaps we have learned a lot. Speaking for myself, I know I haven't had a chance to go through all these questions and make sure I know the answers so I will just have to do my best to answer them off the cuff. This is an important one. Then we will just work our way down the line I think. That is probably the best way to stay organized. I will try not to use too much time.

*If you are a manufacturer of multiple unapproved drugs does enforcement action against one drug for non-safety reasons also target your other products as well, even if those products are not violative in those ways?*

That is a good question and the answer is

yes. If we take action against a firm for GMP violations or for ADE violations, then we are going to go after every unapproved product that that firm makes. I can say that based on the actions that we have taken recently. Pharmakon is one example where there were underlying GMP violations and we enjoined the entire company. This is public. It is on our website and you can see it there. The cases I think bear out that it is perfectly reasonable for FDA to be efficient. It doesn't make sense for us to go to court to teach you how to perfectly manufacture drugs that are illegal. If we have to go to court, then we are going to take action involving all the unapproved drugs.

I do want to just make a couple of overarching comments. I know this probably isn't the workshop that people with unapproved drugs are going to walk out of and feel that this is an easy process, and now that they have sat through the day they can turn around and get approval tomorrow. I think we realize that. On the other hand, and we can talk maybe a little more about this in the Q&A,

not all the drugs that we are talking about here are drugs that are completely unknown to the agency from a regulatory standpoint. There may be drugs that are single ingredients where there is already an approved combination, or drugs where there has already been a DESI proceeding. Bob Temple alluded to some of those this morning. So, I don't think it is necessarily, as Dr. Galson said, always an insurmountable obstacle to get approval but we can talk more about that as we go along.

There are a couple of questions about the status of prenatal vitamins with folic acid. If you want to know the answer to that, I would suggest contacting the Office of Compliance and we can look at specific products and their status. I don't think that is something that I can answer off the top of my head.

*If these drugs are illegal why not remove them immediately? Many companies cannot afford to go through this to get approval. How will FDA assure patient safety if key meds are withdrawn?*

Those are good questions. Well, with respect to the first one, why not remove the drugs immediately; I think we feel that a risk-based

approach is appropriate here. Some of these drugs may, in fact, be medically necessary and we don't want to do anything in the process of the unapproved drugs initiative that is going to be detrimental to consumers' medical needs, which means any time we take action we are going to consider the question of whether we are going to cause a shortage of a medically necessary product. So, that is one reason why not to take action immediately.

Also, we recognize that this issue has been around for a long time and there is a lot of history here, and we feel that the best way to do this is with a stepwise risk-based approach, yet a concerted and concentrated one.

With respect to the question of companies that can't afford to get approval and how will we assure patient safety if key meds are withdrawn, I think if we get to a point where there are medically important drugs that are not approved that are still on the market - I am not sure we will get to that point but if we get to that point,

then we will have to think about what the right way is to bring those drugs under approval. For things like digoxin and levothyroxine I think the agency helped. The agency did some of the research to get the products under approval. I don't now whether we would ever need to do that, but with each of these drugs and each of these circumstances we are looking at the facts and looking at the appropriate remedy given that situation. So, I think we are always cognizant of consumer needs here and making sure that, as I said, we protect the public health in all ways.

*This morning the Commissioner spoke of a collaborative and cooperative effort to achieve the goal of approving these products, yet all I have heard about are the usual pathways. Would the agency consider a DESI type effort?*

Well, I think we have done the DESI type effort as well as monographs and I haven't heard at this point of an option that is viable from a scientific and an economic standpoint. I think the agency is always listening and is never going to say we would never do anything different, but what we have seen and what we have heard so far hasn't

been viable.

*Please explain the de facto exclusivity referenced in the CPG*.

That has to do with the fact that if there are unapproved versions of a drug that has FDA approval and we take action against the unapproved versions, that ends up creating a de facto exclusivity period for the approved drug because for some period of time that approved drug is then the only version of that drug on the market. Kim talked a lot about exclusivities. This is not a legal exclusivity; it is a de facto exclusivity as a result of our taking an enforcement action.

I think what I am going to do, since I have a big stack of questions, is let other people take a turn, answer some questions and I will try to pick out the biggest ones here so I don't use up all our time. Gary, do you want to go next?

MR. BUEHLER (Reads)

*Do you require an ANDA for OTC acetaminophen products?*

No, that is a monograph product so you would just go through the monograph process for that.

*How will FDA deal with an application in which a drug substance manufacturer will not file a DMF and will not provide CMC data to be included in the application although there is ample evidence in the literature demonstrating drug substance CMC are well established and well understood?*

The review of the active pharmaceutical ingredient in an ANDA is a very critical part of the review. Usually this is provided to us in a DMF. I have made numerous presentations where I have stated that we have rarely found a DMF that we have liked the first time around. Even when it does come in a DMF, we usually have multiple deficiencies related to what is in the DMF. An application without a DMF or without any information about how the active pharmaceutical ingredient is manufactured is bound to become found deficient and probably would not be filed. You know, you are the customer of the person who is supplying you the active pharmaceutical ingredient and I am afraid it is up to you to prevail upon them to give you the information or provide the information to us so that we can review your application. It is very difficult to make exceptions in this regard because of the

criticality of the review.

*Do topical products need human clinical trials to submit an ANDA or 505(b)(2)?*

Because topical products are not absorbed to a significant effect so that we can measure the active ingredients, usually they require some type of human clinical trial. For steroids you can do the blanching study. You can find out in our guidance that you can do a blanching study for topical steroid products. But for the other products, as I said, I recommend that you actually request from us the bioequivalence requirements for the particular product. Some are fairly straightforward and some are not. Especially for some of the newer products the bioequivalence requirements are not that straightforward so I would recommend you get specific instructions for those.

*Do all drugs with FDA approval labeling appear as drugs at FDA website? Is drugs at FDA the same as the "Orange Book" online? Please explain why Robitussin products are missing from Drugs at FDA.*

Well, I don't do *Drugs at FDA*. I do the "Orange Book" and I do not know the answer to that question. I don't know if anyone here is more

familiar with *Drugs at FDA*.

MS. AUTOR: I can address that question I think. *Drugs at FDA* actually derives its data from the "Orange Book," as I understand it, and then some. So, *Drugs at FDA* lists all FDA approved drugs. Now, you can search *Drugs at FDA* for an approved drug and not find it there because it may actually be listed under a different company's name. The *Drugs at FDA* is going to list the sponsor but you may be looking at a drug that has the name of the private label distributor, or something to that effect. But the drug itself should appear at *Drugs at FDA* if it is FDA approved. If it is a monograph product it is not going to show up with *Drugs at FDA* because monograph products don't have affirmative approval from FDA. They are made in accordance with the recipe book that is in the monograph.

MS. DETTELBACH: I have a lot so I will go through some and then let someone else have a turn.

*Will the five-year exclusivity right be granted if the API has been marketed for approximately 50 years but has not been covered under a prior NDA or ANDA?*

Yes, if it has not been previously approved under 505 either alone or in combination

it is eligible for five-year exclusivity.

*If a 505(b)(2) application is filed for an unapproved drug and the application contains clinical data would the drug product receive three-year market exclusivity if the application is approved, statutory exclusivity? If so, how does this market exclusivity affect other like unapproved drugs on the market? How can market exclusivity be upheld and enforced with other unapproved drugs on the market?*

If it is filed and contains new clinical data essential to approval it is eligible for three-year exclusivity whether it is in a 505(b)(1) or a 505(b)(2) application.

How does this affect other unapproved drugs on the market? As I think I said in my talk, three-year exclusivity is a bar on approval. So, unapproved marketed drugs aren't directly affected but the compliance priorities suggest that once someone is approved the unapproved drugs become a compliance priority, to be removed from the market.

*If tacrolimus is approved for the innovator as an oral capsule, injectable and topical ointment, can another company get an approval for a sublingual using info from the innovator's labeling? What kind of studies for a 505(b)(2) might be required? Any exclusivity? Then, if they had orphan exclusivity can a sublingual be submitted?*

Yes, you can get an approval for a

different dosage form. You can do that under 505(b)(2) or, if pediatric studies aren't required, you may be able to do that under a suitability petition.

What kinds of studies will be required? I can't speak to that directly but we do say that for 505(b)(2) applications that to the extent they are the same as a previously approved product you can rely on the finding of safety and effectiveness for that product. We don't rely on the individual studies in the NDA but we rely on the finding that a particular drug product at a particular strength and a particular dosage form is safe. Then you are required, as the applicant, to demonstrate the safety and the effectiveness of any differences from that product. So, in this case if the only difference is a difference in dosage form, then you need to demonstrate that that dosage form is also safe and effective. Other people might be able to speak more specifically as to what that would require.

Is it eligible for any exclusivity? It

depends on which studies are done. If it is just bioequivalence studies or bridging studies comparative bioavailability, then that would not be eligible. If we require clinical studies you could get exclusivity for those.

If they had orphan exclusivity can the sublingual be submitted? It depends on what the orphan exclusivity is for. If you are submitting for the same moiety for the same indication, then we cannot approve that application for seven years, until the orphan exclusivity expires. If you are submitting it for a different indication, the orphan exclusivity doesn't block that. You can also make an argument of clinical superiority, either that it is more safe or more effective or, as I said, a major contribution to patient care. If you succeed in those arguments the orphan exclusivity will not stand in the way of your approval.

Maybe this will be the last one for now.

*If company A does clinical trials leading to a 505(b)(2) approval, does clinical exclusivity prevent company B from doing clinical trials for 505(b)(2) approval, the same drug product; the same indication?*

If they receive three-year exclusivity, then drug product B is blocked for three years for seeking approval for the same conditions of use. They can submit an application in that situation but we can't approve it. If they receive five-year exclusivity because, for example, it is the first the moiety has been approved, then we can't even accept the second application for review for that moiety.

DR. JENKINS: Just one thing to add onto that, I think the point of the question, Kim, is can the second company do the same studies that the first company got approved for--

MS. DETTELBACH: Oh, I see.

DR. JENKINS: So, can you overcome the exclusivity by doing your own studies?

MS. DETTELBACH: That is actually an evolving area of the law, but our current thinking is that you cannot do your own studies to overcome three-year exclusivity if the conditions of approval would be the same.

DR. JENKINS: I just wanted to make one

comment. Gary I think had a question earlier about acetaminophen. I think there may be some NDA applications over-the-counter that include acetaminophen. So, any of those, obviously, could be subject for an ANDA. So, if it is approved under an NDA it can be subject of an ANDA but if it is marketed under a monograph you can't submit an ANDA. You wouldn't really need to. You could also do the monograph yourself.

I have kind of a hodge-podge of questions here, some that I can answer and some for which I am going to enlist some other people, if they want to comment. The first one is

*Would FDA consider a different PDUFA fee structure for former DESI products, especially considering that most are not exactly block-busters?*

[Laughter]

I presume the questioner is not asking about a fee structure that would have higher fees! This is really a congressional issue. The user fee standards are set in the statute so the statute outlines what the fees are and how they are assessed and collected. So, this would really have

to be something that the Congress would need to address and I really can't speak to any agency position on what the administration view might be on a lower fee structure for unapproved marketed drugs. I really can't comment on that.

I would note that the user fee program is authorized in five-year cycles. We are currently in the fifth year of the third five-year cycle for the user fee program, and the program has to be reauthorized by Congress by the end of September or it goes away. So, the agency will be submitting for congressional review soon proposals for what PDUFA-IV should look like but I can't speak to whether this might be something that Congress would decide to address in the PDUFA-IV discussions.

When you say ten-month review for an NDA, is that including the 60-day review for the filing or is that a total time of 12 months?

The filing review is included within the timelines that Kim mentioned earlier so that is included. We have either a goal of completing a review in six months for a priority application or

ten months for a standard application so it is not an add-on to the 60 days. We start counting from the day your application is submitted.

One thing I do want to note here is that our goals under PDUFA are for review of the application within the time frames. They are not approval goals. People often mistake and say that we have goals to approve 90 percent of applications in ten months. That is not the case. We have goals for completing our review of applications in ten months 90 percent of the time for standards, for example.

This is one that I actually probably could have written myself.

*What additional resources are available in the Office of New Drugs to handle what would be a significant increase in the number of pre-IND meeting requests? Will you be monitoring time frames for granting pre-IND meetings, as they are currently getting harder to schedule?*

It is a very relevant question. We have, over the last several years, experienced a significant growth in our workload in multiple areas that has gone far beyond any increases in staffing we have seen. So, our divisions are

really facing a crunch in their workload and their ability to take on new projects.

With that being said though, we do have user fee performance goals for meetings with industry so that guidance that Kim Colangelo mentioned to you earlier is, in part, to outline how we meet with sponsors under PDUFA products and meet our performance goals. We follow the same procedures and follow the same goals for non-PDUFA products as well. Although, if you were coming in for a pre-IND meeting for an unapproved marketed drug, that is essentially a PDUFA product because INDs are considered under PDUFA even though they don't pay a separate fee.

It is a significant concern that I have. It is a concern that all my divisions have. We are already failing to meet our performance goals for meetings. We have a 90 percent performance level and we are currently in the mid-80s in meeting our goals for scheduling and holding meetings and getting the meeting minutes back to the sponsor afterward. We have seen a dramatic increase in our

meetings even before this initiative so it is a concern but we will continue to do our best to consider these requests and schedule the meetings in a timely manner. One of my hopes is that you will end up in the monograph process or in the ANDA process -

[Laughter]

- And that few of you will make it to the NDA process! But the ones that do need to be NDAs, we are there and we are going to do our best to work with you to help you get to the goalpost.

A couple of these actually overlap with David Jacobson-Kram and I know he said he didn't get any questions so we will share these, David. The ones that say that we are doing a good job I will take and the ones that are critical I will give to you!

[Laughter]

The first one is:

*In a number of instances for 505(b)(2) submissions for, say, a different dosage form the pharm/tox reviewers have asked for updated preclinical studies because the reference drug was approved such a long time ago. Why would such studies be necessary if the reference*

*product has been approved for a long period of time and the proposed 505(b)(2) is for a common indication and dose or exposure as the reference product? There needs to be consistency among the divisions.*

Well, I agree totally with the last statement. There needs to be consistency among the divisions and that is part of what I have tried to do in my five years in the job of OND director, try to move us towards being more consistent, or at least being consistently inconsistent for a reason. You know, we can't always be a recipe but we have to have valid reasons for why we are doing things differently.

Let me just say that in general our approach to 505(b)(2) applications is that you are relying on our previous finding of safety and effectiveness for the product and you are being asked to demonstrate the safety and effectiveness of your product in ways that it differs from our previous findings. We all know that the regulatory standards and the science evolve over time so invariably if you are coming in, referencing something that was approved many years ago or even just a few years ago you might find that the

standards have changed. And, our reviewers are inclined to want to ask you to meet 2007 standards.

Our stated approach though is that we don't necessarily, as a rule, as you to go back and fill in boxes that weren't filled in by the original product, or do new studies that were done by the original product unless there is a valid scientific reason for us to ask for that. Reasons might include maybe the original product was approved and used only in adults and now you are asking for it to be approved for use in children. That might trigger a legitimate need on our part to assure that new tests are done to assure the safety for that new population. The previous product may have been approved for short-term use and you may be asking for chronic use. So, the fact that the original approval didn't have carcinogenicity testing might have been appropriate for short-term use. You may be asking for long-term use and we would feel that our previous finding doesn't carry over. So, there are differences that warrant asking you to do new studies.

It is also conceivable that the way studies were done in the past might be considered now to be scientifically invalid so we may not feel comfortable that our finding was valid, although that gets into a more tricky area.

The problem reviewers face is that they are naturally inclined to ask you to do what we would expect a new product in 2007 to do. So, we constantly need to look carefully at what we are asking you to do and what our justifications are. We say repeatedly that it shouldn't just be a recipe or a checklist, that they have to do all the things on the checklist. We have to be able to justify why those things on the checklist are needed. I always point to the fact that if this were a generic drug, they wouldn't do any of this.

It doesn't even come in as a question because generic drugs are approved based on showing that you are bioequivalent to the reference listed drug and we don't revisit whether the carcinogenicity studies were done in the past.

So, if you are having these situations

where you are uncomfortable with what you are being asked to do, I think your first recourse is to further pursue those questions within the division, with the division director. You can talk to the office director. Also, David is our senior pharmacology/toxicology expert for the Center and he is another resource. David, do you want to speak more to this?

DR. JACOBSON-KRAM: I guess I would just reiterate what John said. You know, if a reviewer, in looking at a 505(b)(2), goes back and sees that perhaps some aspect of the nonclinical studies was either not performed, or performed to a standard that we would now consider woefully inadequate, their inclination is to try to fill those data gaps to assure safety. But we have made it very clear in various venues to pharm/tox reviewers that unless there is a change for the indication, duration of treatment, things like that we do not ask for additional preclinical safety data.

So, again to reiterate what John said, if you find yourself in a situation where you are

being asked to fill these gaps, I just wouldn't mindlessly go ahead and do it. There are recourses and we would be happy to talk to you about it.

DR. JENKINS: It is one of the most challenging areas that we face because, you know, reviewers are inclined to want the best possible data for what they are reviewing in 2007. But if you are hearing something different and it is not adequately being justified to you as far as a reason we need to ask you to do that study, pursue it further within the division within the office. There are formal dispute resolution procedures that you can follow. Those sometimes are successful in granting the relief that the sponsor is requesting.

This is a related question and maybe the same question in many ways. It says:

> *So far three out of three divisions have, quote, strongly, unquote, recommended that we do preclinical carcinogenicity work. Is it safe to assume that all unapproved drugs will require these types of studies?*

No, I don't think it is safe to assume that all unapproved drugs will require those studies. What I said in my introductory remarks is

that each one is going to be done on a case-by-case basis, looking at what do we know and what are the indications; what are the uses, etc. If you are an unapproved marketed drug and you are not referencing - for example, a never approved molecule - then it is going to be very unlikely that you are going to be able to pass through the NDA process without doing at least some of the work that David had on his slide. He did point out that previous marketing history can obviate the need for some of the studies but you really can't get around others, such as genetic toxicology information, maybe carcinogenicity depending upon your indication, reproductive toxicology, etc. If you are referencing something that has already been approved by the agency, then you fall into the conversation we just had. I will stop there.

DR. MEYER: I only have one question and it regards the timing of submission of safety data. The question reads:

> *Where long-term clinical safety data are required will your divisions accept the six-month data or interim data at the time of the original filing, followed by the 12-month*

*data, presumably at the safety update per the ICH guidance, or will all 12 months of data be required at the time of first filing?*

Apparently the questioner has gotten different answers. But the answer should be that all 12 months of the data are required at the time of filing. The understanding under the Prescription Drug User Fee Act is that we would do a complete review within a certain time frame of a complete application and a complete application should have all the data necessary for us to do our findings or evaluation, with the exception of the safety update which is not meant to really inform or contain necessary safety information but is really meant to sort of update the safety evaluation for many ongoing studies that were being done for other indications or perhaps foreign marketing experience, and so on.

So, the answer is that the application should be complete in all regards at the time of filing. I guess the other thing that can come in after the application are some updates to the stability data as well. So, to the degree that my divisions have given inconsistent answers, I hope

some of that is historic and I will make sure that it is.

DR. JENKINS: That is another issue that is near and dear to my heart. In the past we were more liberal in answering yes to that question back in the days when we, for example, had 12 months to review a standard NDA. But as time has passed and our timelines have gotten shorter and also our workload has gotten greater, we simply cannot continue to not honor the original agreement under PDUFA which, as Bob said, was complete application; complete review within a given time frame; and a complete response, either an approval or a list of all the deficiencies. So, in going forward, my advice to all of the divisions in OND is that the answer to that question is "No." We need complete applications so that we can mange the application during the review cycle, to get our work done in a timely manner and, hopefully, avoid multiple cycle reviews.

One of the areas that is very inefficient for us, very inefficient for you and the public are

multiple cycle reviews to get to an eventual approval. We are currently essentially drowning in resubmissions from multiple cycle reviews and we have to get ourselves out of that, and you share some of the burden for that, which is to submit a complete application. You will see, when some of the proposals for PDUFA-IV agreement are shared publicly, some ways that we have tried to put some teeth in there to try to further enforce the idea of complete applications at time of submissions.

DR. MATHIS: My first question is:

*What is the process and timeline for a suitability petition regarding a change in dosage form of an ANDA product in the Division of Pediatric and Maternal Health Staff?*

Well, the suitability petitions actually come in to OGD and they notify us when they have a suitability petition that may trigger PREA. We look at it and see if it does trigger PREA. So, it is any one of those five conditions and, of course, dosage form change is one of those five conditions. We then look at it and see if there are studies already done and what the labeling is for pediatrics; what informational needs are for the

labeled indication; and whether or not pediatric studies would be required. At that point we actually discuss it with the pediatric implementation team which meets every two weeks so we, hopefully, don't cause a major delay in having the suitability petition evaluated by the people that sit on the suitability petition panel and recommend against or for approval of the petition.

Mr. Buehler, do you know the specific time frame for that? It usually takes about six weeks to work its way through the process. But, again, just because it is a suitability petition doesn't mean that we would always say that the suitability petition couldn't be approved. We would do the same thing we do for NDAs. We would either grant a waiver, require studies or give you a deferral. But I think it is probably about a six-week process.

MR. BUEHLER: The suitability petition process is really variable. I mean, there are many more variables other than just whether PREA is involved or not, although that really is a major

issue with suitability petitions. If, in fact, the decision is made that the change would trigger a PREA, usually our recommendation is that you take your proposal to New Drugs with a 505(b)(2) application because there you are able to get a waiver or a deferral on the particular application or the particular change, whereas we cannot give you there as an ANDA and we will just refuse to file your application when it comes in.

As far as the timing of citizen petitions, the meetings are difficult to schedule sometimes because the people on the petition committee are so very busy and we have to get a quorum for this. We are actually working on that particular issue right now so that we can get better attendance at the meetings. But, again, there is just a myriad of issues that come to us in the suitability petitions and if any issue pops up in a meeting where there is concern expressed by one of the suitability petition members, it can delay your application for an indeterminate amount of time.

DR. MATHIS: The next question is:

*After October 7th, what will be required while the new regulation is being decided?*

We don't know if or what the new regulation will look like. In general, if you have a written request that is alive and in your hand at the time that the law sunsets, then we will honor that written request. So, if you come in with studies per the written request you still will qualify for exclusivity as long as you had a written request before October 1, 2007.

As far as the requirements under PREA, we will probably, in any action letters, notify you of the potential for Congress to reenact requirements similar to PREA but I don't believe we would have the jurisdiction to require them at that time if it sunsets with a gap. Last time that FDAMA expired, actually BPCA passed so closely on its heels that we didn't have a big problem with a gap but we did have to address some applications that came in, in the interim.

*Is pediatric exclusivity restricted to the pediatric indication?*

The answer to that is that for the first period of exclusivity, pediatric exclusivity actually applies to the entire active moiety. So,

no, it is not pediatric exclusive. If you come back in a second time and get a second period of pediatric exclusivity, that period would be exclusive to the pediatric indication.

*Can a PREA waiver be given to an OTC monograph product that has an approval?*

The OTC monograph usually gives the ages and conditions of use so we wouldn't require new pediatric studies. So, yes, you could have a waiver. And, again, it would have to trigger PREA with one of the five. No, I don't think it would trigger PREA. No, you won't get a waiver but you won't need one either.

*How is the six-month exclusivity period arrived at? Was some complex government formula used to calculate the six months? I am sure it was. Kim, do you have any insight into that?*

MS. DETTELBACH: Even though Congress came up with the six-month period, there has been discussion and there was discussion about whether it should be pegged to, for example, the value of the exclusivity, high dollar drugs maybe get a shorter period. That was not enacted and, frankly, that would be very hard for FDA to implement. But

there has been talk in the reauthorization of both shortening and lengthening the period, depending on which side you are talking to. Congress chose that I think somewhat out of the blue, randomly.

DR. TEMPLE: The answer is obvious. It is not too short and it is not too long; it is just right!

[Laughter]

DR. MATHIS: I am going to answer the last question because it is quick.

*Please expand on the ability, if any, to rely on dosing studies to meet PREA requirements.*

If the only thing that is needed is dosing information then, indeed, only dosing studies would be needed to meet the PREA requirements. That would depend on whether or not we were able to extrapolate efficacy or if there was data available about the safety and efficacy in the pediatric population.

DR. LOEWKE: The first question is:

*Are communications between a company and the FDA regarding any specific unapproved drug considered business confidential?*

I would say yes to that. The second question:

*Should a sponsor request the presence of the unapproved drugs coordinator when meeting with the review division?*

The review divisions have been notified that when unapproved drug requests or applications and even requests for meetings come in that they are to routinely invite me. However, they are very busy people. Sometimes this may fall off their radar screen. So, your request or at least a cc to me of the pre-IND request is helpful just to make sure that they invite me. Unfortunately, I can't attend every meeting. I try my best to be present. If I know I am not going to be available for the industry meeting I certainly push to make sure I have been involved in the pre-meeting.

MR. JONES: For those of you who don't have any questions, I will be glad to share some of them with you! Let's see, these are kind of closely related I think. The first question is:

*What is FDA's decision on user fees for generic drugs, and why can't FDA charge fees for generic drug applications and expedite the drug approval process?*

Great questions! The decision on either of these for generic drugs is you don't pay.

However, I think what the questioner is trying to allude to is, for the last 20, 25 years people have been talking about, you know, should generics pay user fees or not. I think depending on who you talk to, you get different answers. I think that FDA would probably agree that that would be a good thing. I think if you talked to the generic industry, you will get differing opinions. So, if you read the press you can see what their answers are. I think that kind of explains both of those.

Gary, did you want to chime in at all?

MR. BUEHLER: No, you did a nice job!

MR. JONES: This one is for the small business.

*If a company stays under 500 employees are they always excluded from fees?*

Well, they are not always excluded from fees. Basically, the small business waiver is for your first application only. It doesn't include product and establishment fees. It only includes that first application. So, you can grow and you can be 750 but you only get that one shot for that small business waiver. Again, that small business

waiver doesn't include the annual product and establishment fees; it is just that first application.

The second part of the question that I can also answer says:

*Is there a small business exemption for annual product and establishment fees?*

The answer is no. (Next question)

*If a company has only filed ANDAs historically, can they waive the user fee for its 505(b)(2) NDA?*

Again, that kind of goes back to what is a human drug application. So, if all you have submitted are 505(j)s, then that first (b)(2) that you submit, you know, you can apply for that small business waiver because it is for the first human drug application and you and your employees are under 500.

*If a company uses a contract manufacturer to file a 505(b)(2) does that use up the contract manufacturer's fee waiver, or will that be used for the initial company? Can a contract manufacturer file on behalf of another company and have their fees waived still?*

What it comes down to is it is the application that will get their fees waived and it is the application or that applicant's affiliates.

So, if the CRO is an affiliate, then they have used that up. If the CRO is the application holder they can certainly request a waiver. But the second one through the door that the CRO wants to do, they won't get waived. So, it is the small business waiver, first application, for you and your affiliate.

The second part of the question:

*Can a contract manufacturer file on behalf of another company and have their fees waived still?*

I mean, you could have a CRO kind of be your agent and they can submit a waiver request on your behalf.

I think this is supposed to be:

*Does a contractor manufacturer making the final dosage form pay establishment fees? Any additional requirements or fees for overseas manufacturers? Any fee for submitting a DMF?*

Again, it comes back to the application holder. The application holder is responsible for the establishment fee. We are not going to be sending a bill to the manager that is in charge of the plant. We are going to be sending the bill to whoever the application holder is.

MS. AUTOR: Mike, I think we are running low on time. Bob, do you have any questions in front of you?

DR. TEMPLE: A few.

MS. AUTOR: A few? Anything that you think is a must answer? I have one or two that I would like to try to just touch on quickly at the end.

DR. TEMPLE: A must answer? I have a profound philosophical one. All right, no philosophies?

MS. AUTOR: I will tell you what, while you read your questions I am going to exercise the moderator's privilege and see if I can spend 60 seconds going through a few that I feel I really would like to answer.

*Does FDA have jurisdiction over drugs that are not traded in interstate commerce?*

This may be some confusion I caused by an earlier answer. The short answer is yes. FDA has jurisdiction based on components that have traveled in interstate commerce and these days it is pretty much unheard for there to be a drug without a

component that has traveled in interstate commerce. A drug that is unapproved is also going to be misbranded and, therefore, FDA would have jurisdiction over that.

*How can someone search on the FDA websites to determine if an unapproved drug product is considered pre-'62 by FDA? I am particularly interested in cough and cold products that are marketed as Rx only without NDAs. Many match OTC monographs although their labeling is for a non-OTC monograph population. However can the status of these products be determined?*

Well, I can tell you the status of these products. In all likelihood they are illegal. As we said, we think it is highly unlikely that anything is grandfathered or GRAS/GRAE.

The next question also relates to this, which is:

*Can a product that qualifies under an OTC monograph be marketed instead as a prescription product under any circumstances including, for example a subpopulation?*

The answer is sure if it has FDA approval. But a product that is covered by an OTC monograph has to be marketed OTC in accordance with that monograph.

*Is it possible to get a drug listing number or code* [I think that means an NDC number] *without an approved NDA or ANDA?*

The answer is currently yes, but as folks know we issued last year a proposed part 207 which will implement electronic drug registration and listing. I know there has been some discussion of whether, under that system, there will be NDC numbers for unapproved drugs. So, the answer is currently yes but it is not as clear in my mind what is going to happen. Finally:

> *How will FDA deal with the case of one manufacturer, quote, changing their position or otherwise choosing to file an NDA, probably 505(b)(2), in an attempt to gain the proposed effect of market exclusivity? This would be an obvious manipulation of the NDA process and statutory protections to inappropriately delay competition.*

What I want to say to that is that if a product is, in fact, grandfathered, then we are not going to take it off the market because you would be entitled under the law to market. As I said, we think it is unlikely that something is grandfathered. So, somebody coming in for an NDA when your product is grandfathered wouldn't allow us to take your product off the market but, again, we think that is really unlikely. In all likelihood, all products are marketed illegally and

if one person were to come in and get approval and we were to take enforcement action against the unapproved ones, the unapproved ones would come off the market.

Bob, do you have one or two, and then we will wrap up?

DR. TEMPLE: I have it down to two. One of them hasn't really come up, and that is:

*Are there any nutritional products that are classified as drugs? If so, which ones?*

Well, I am not going to be able to give you a list but the rule on dietary supplements and nutritional products is defined under DSHEA and it says whether it is a drug or not depends on its claim. If it makes a drug claim that it is to treat disease, then it is a drug and many nutritional products could make such claims. How much we are going to do about these things is another question.

We have actually just approved a green tea extract for I think oral ulcers - I don't know, for something. Oh, genital warts? Well, I had the wrong orifice!

[Laughter]

I knew it was something ulcerative. Anyway, these things are frequently studied under an IND. St. John's Wort is studied for depression. So, there is a potential for these things to be drugs. And, if somebody is marketing them as drugs they should be filing applications.

The last one, as I said, is philosophical but it does raise a question.

*A Nobel Prize winner economist once stated that the best indication of the effectiveness of a product is its frequency of repeated use. If that is true, why don't we give any credence to a long period of use?*

The short answer is that is not what the Food, Drug and Cosmetic Act thinks and the DESI process itself really rebuts the Nobel Prize winning economist. One of the widest used drugs for irritable bowel syndrome, which had no good treatment, were these combinations called anticholinergics and anticholinergic sedatives which were studied in what must have cost hundreds of millions of dollars in large, pretty good trials, every one of which failed to show a

contribution of either component. If there had been a contribution of the combination but you couldn't show each component, then you could understand why people might have felt good about it. Every one of them failed completely, every single one. So, the fact that there is long-term use doesn't really tell you anything and that is why we don't pay any attention to long-term use as evidence of effectiveness, plus lots of other reasons.

MS. AUTOR: Thank you to all the panelists and thank you to all of you for persevering through the day.

[Whereupon, at 4:30 p.m., the proceedings were adjourned.]

- - -