The FDA Process for Approving Generic Drugs

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Hi. I'm Gary Buehler, Director of FDA's Office of Generic Drugs, and today we are going to discuss the FDA process for approving generic drugs.

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Do you know that generic drugs are safe and effective alternatives to brand name prescriptions? They can help both consumers and the government reduce the cost of prescription drugs. Currently, about 50% of all prescriptions dispensed are generic and they save an average of about $50.00 for every prescription sold.

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Tracing back to the beginnings of the generic drug program, the Hatch-Waxman Amendments of the Federal Food, Drug, and Cosmetic Act were passed in 1984. This was considered one of the most successful pieces of legislation ever passed and, in fact, created the generic drug industry as we know it today. It increased the availability of generics from about 12% in 1984 to 44% in the year 2000, and close to 50% today. This was a compromise legislation benefiting both the brand and the generic firms.

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For the generic firms, it allowed them to rely on the findings of safety and efficacy of the innovator drug after the expiration of certain patents and exclusivities. In other words, the generic drug firms did not have to repeat the expensive clinical and pre-clinical trials that have to be done for a new drug application. For the innovator industry, it allowed certain patent extensions and exclusivities that were not available previously.

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Going over a comparison of the review required for a new drug application or an NDA to the review required for an abbreviated new drug application or ANDA, many of the points are the same. Chemistry, Manufacturing, and

Controls are rigorously reviewed by both the new drug reviewers and the generic drug reviewers. Labeling is also reviewed and has to be identical in most aspects. Testing is identical for the new drug applications and the generic drug applications. The same FDA field inspectors inspect the manufacturing facilities for generics and for the innovator products. These facilities must be up to date with respect to good manufacturing practices or GMPs and must have documentation that they are able to manufacture the products for which they have applications. The differences in the applications, as previously stated, are the clinical studies and animal studies required for the new drug application and the bioavailability studies that have to be conducted to define the drug's interactions and adverse events. A surrogate for these studies is the bioequivalence study that has to be submitted for the ANDA. Showing in the bioequivalence study that the active ingredient is absorbed at the same rate and extent as the reference product allows the generic to rely on the findings of safety and efficacy of that product.

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The general requirements for a generic drug application or ANDA are labeling, chemistry and microbiology, bioequivalence, and legal. We will go into these in a little more detail.

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How do we assure the quality of a generic drug? As stated above, we have five steps to the review process that are identical to the NDA process. Bioequivalence for complicated products is discussed with the same staff who have reviewed the brand name product.

FDA has extensive experience with the innovator drug product. Many times this product has been on the market for many years. So in tapping from the experience from the new drug review, we have experience in reviewing adverse events and clinical experiences with the drug product. There is also a great amount of scientific literature on the drug product that we are able to access. Lastly, the product is known to be safe. Again, with its years of marketing history, there is no question about the safety of the drug product.

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This is a schematic of the generic drug review process from receipt of application until its final approval. The applicant submits the application to us and it goes through an initial filing review to make sure the application has all the requisite pieces to be reviewed. With respect to any patents or exclusivities, this group also assures that all initial legal requirements have been addressed. From the filing review, it is sent to chemistry and microbiology if necessary for sterile products. It is sent for a labeling review and to bioequivalence for a review of the bioequivalence study. We also request certain plant inspections and manufacturing inspections to make sure that the manufacturing sites and all other ancillary sites are in compliance with good manufacturing practices. Each of these disciplines completes their review and once everyone has resolved any deficiencies identified in the application, the product can be approved.

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What are the requirements for a generic drug? A generic drug has to have the same active ingredient(s), the same route of administration, the same dosage form (tablet, capsule or injectable), and the same strength, and the same conditions of use when compared to its reference listed drug or corresponding brand name product.

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The labeling has to be the "same" as the brand name labeling. The generic applicant may delete portions of the labeling protected by patent or exclusivity. The labeling may differ in certain excipients, pharmacokinetic data, and how supplied section. The generic does not have to have the same bottle sizes as the innovator product and the generic can also differ in product-specific characteristics.

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Chemistry is an important aspect of the generic product review. The chemist looks at the components, composition of the generic product, to make sure that the formulation

is stable and in compliance with our regulations and standards. The chemist looks at all the manufacturing and controls of the product, carefully reviews the batch formulation and records, and the description of the facilities to make sure they are in compliance with good manufacturing practices. The chemist carefully looks at the specifications and tests to make sure that the impurities are within our certain limits and that the tests are appropriate for the particular product. Packaging is reviewed to make sure it assures the stability of the product and the stability is assessed to assure that the shelf life of the product is appropriate.

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We have manufacturing and compliance programs to assure the quality of the marketed drug products. We have routine surveillance of marketed drug products to make sure they are, in fact, what they say they are. We have routine inspections of all manufacturing sites to make sure that they are in compliance with current good manufacturing practices. The pre-approval manufacturing and testing plant inspections also assure that the actual manufacturing site is capable of manufacturing a particular product.

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Approved Drug Products with Therapeutic Equivalence Evaluations is the official name of what we affectionately call the Orange Book.

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The Orange Book lists all FDA approved drug products, that is, NDAs, over-the-counter products, and abbreviated new drug applications or generic products. The Orange Book also contains therapeutic equivalence codes. Any product that has an A prefix is considered a substitutable product by FDA. Any product that has a B prefix has not been proven to be equivalent and, therefore, is not substitutable, although it is a safe and effective product for use. The Orange Book also has the expiration dates of certain patents and exclusivities and it denotes the reference listed drug for each particular brand name product. The generic companies usually use this information to determine what reference product they have to do their bioequivalence tests on.

And now I would like you to hear from my colleague who will discuss the bioequivalence requirements for generic drug products. Thank you.

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Hi. I'm Dale Conner, Director of the Division of Bioequivalence, Office of Generic Drugs, and I am going to discuss bioequivalence and how we apply that science to assure therapeutic equivalence of generic drugs. Bioequivalence on its face seems like a very simple concept where you compare two formulations containing the exact same amount of an active drug in the same dosage-form; you simply determine whether that formulation supplies that drug to the body in an equivalent manner. As you will see, how we go about doing that and assuring that equivalence is often misunderstood. It is not only confusing to laymen and consumers but to medical professionals as well. Even people within the FDA sometimes get confused about this.

I'm going to start out by giving a simple definition of bioequivalence. There are, perhaps, many definitions and this one, I believe, is adapted from the regulations: "Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under different similar experimental conditions." This encompasses a lot of explanation in that, under similar conditions, when we give these two pharmaceutically equivalent products to the same individual patient, the patient should absorb the same amount of drug, or very close to the same amount of drug, and absorb it at the same rate.

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What is the purpose of bioequivalence? From the Generic Drugs perspective, in the end, we would like a generic drug that is substitutable for a reference or brand name drug. This substitution could be implemented without any additional prescriber intervention. That means that a patient could walk into their pharmacy one day, having received and been very well controlled on the brand name drug, or perhaps even another generic drug, and the pharmacist could substitute an A-rated FDA approved generic drug to that patient for their next month or so of drug

therapy, and we would effectively see no objective difference in the therapeutic outcome for that patient. There would be both no change in efficacy and no greater incidence of side effects. So we look at both the efficacy side and the side effect side.

In effect what we are aiming for by doing bioequivalence is to assure therapeutic equivalence of these products. Bioequivalent products and therapeutically equivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring other than what you would ordinarily do for that patient on that particular medication. The most efficient method of assuring therapeutic equivalence in the end is to assure that the formulations perform in an equivalent manner.

This brings up one of the important points that are often misunderstood about bioequivalence. Bioequivalence is really a test of in-vivo formulation performance. What we are interested in is that two manufacturers or sometimes the same manufacturer has made two separate formulations containing exactly the same amount of exactly the same active drug and they want to test or be sure that those products perform in the in-vivo situation in a close to identical manner.

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This slide is a simplified schematic of what happens when one gives an oral dosage form. I'm going to spend a little bit of time on this because this lays out the areas of concern or what happens when you give an oral product. It also serves to explain why we do certain things to assess sameness or bioequivalence and why certain other options at our disposal are not the best choice.

If we go from left to the right of this slide, we see that we start with a dosage form. It could be a tablet or a capsule. If it's an oral product, we give that tablet to a patient, they swallow it, and the drug, which is in the solid form in the GI track, goes into solution. That is a critical step. How that solid form falls apart, releases its drug, and goes into solution is a critical step as far as formulation performance.

In effect, as you follow this schematic further on, it's the only step in which we as regulators and the pharmaceutical industry as manufacturers really have any control. The rest of the steps in the process are patient-related. In other words, the drug is absorbed and the natural disposition of the patient or the group of patients controls how the drug is distributed and how eventually it gets to the site of action. The thing that we really have control over and the thing that we as a regulatory agency want to assure is that the first step is equivalent between these two products so that the two tablets transition from the solid to the solution state and become available for absorption in the same manner. That's why bioequivalence as we use it is a test of formulation performance. The formulation performance we are talking about is in that very first step in the transition from a solid dosage form to a drug in solution, which is then available in the GI track for absorption.

As we follow this through, that's what we're really concentrating on; making sure that two products by two manufacturers or even two products by the same manufacturer do that step in an equivalent manner.

As we see, the drug gets into solution and it's then available for absorption through the gut wall and absorbed into the blood. This is over simplified because there are a number of steps in between. From the gut wall to the blood, there is often passage through the liver and I've simplified that here. However, it appears in the blood directly after absorption. Then the blood carries it to the site of activity and subsequently the drug does what it is designed to do at the site of activity and we eventually see a therapeutic effect or some other pharmacologic effect as well, even an adverse event or a side effect. We would also see that as well after the drug got to its site or sites of activity being carried there by the blood. Thus we have described in a very simple way what happens after we give a solid dosage form to the point where we would actually see an effect.

The question is what would be the best way of assuring that these two products perform in the same way in vivo? I can't simply give this solid dosage form to people and look down in the GI track and see how it's dissolving or becoming available. That is really not exactly a very practical way to approach things. I want to go down the

schematic and say what's the most sensitive point that I can actually measure drug leaving the dosage form and entering into the body and then subsequently arriving at the site of activity and causing a pharmacologic effect.

The first step where I can reasonably do that is the blood. The blood acts as a carrier, an intermediate between the drug being absorbed and the eventual effect. The blood, as we all know from clinical practice, can be easily sampled. It is used for a variety of different types of clinical monitoring and quite a few blood samples can be taken over time if you really need to. The drug appearance in blood and the pharmacokinetics of that drug in blood has some very favorable characteristics for answering the questions we're posing about the dosage form performance.

Often when I speak to clinicians, the question comes up that it's all very nice to measure things in the blood, but what I'm really interested in is the eventual therapeutic effect. Why don't you just measure that directly? There are certain types of products where we have to do that because the blood is either not relevant or the drug doesn't appear in any measurable quantity in the blood or for other reasons. So we have to use either pharmacodynamic measures or clinical measures, which are what was used to assess the drug efficacy originally anyway. When you look at the characteristic of those measurements, there are some problems. First, the appearance in the blood is very close to the event that we're looking at. There are not too many steps in between that add variability, because each step that you pass through increases the cumulative variability. For blood concentrations, most of the relationships between blood or plasma concentrations and dose are linear. If the dose increases or decreases a little, we see a linear increase or decrease in the plasma or blood concentrations. Even when it's non-linear elimination pharmacokinetics, in effect it actually becomes overly sensitive to telling the differences between products. In that situation, a small change in delivered dose results in disproportionally large increase in plasma concentrations. So the measurement of drug appearing in blood allows us to fairly accurately tell what the relative bioavailability of the dosage form is between two or more formulations.

If we consider clinical effects, the pattern of a clinical response, if we remember our pharmacology, is usually an S-

shaped or sigmoidal dose response curve. What we're really looking for when we look at differences in bioequivalence is if two pharmaceutically equivalent products, containing the same amount of a drug, effectively deliver a different dose. What we're looking for ideally for a bioequivalent product is that the product should deliver the same dose at the same rate to the body. So putting it on a dose-response curve is valid. We see that the response that we're getting in a therapeutic response is not linear related to a change in dose. It's more S-shaped.

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If we go to the next slide and see that relationship blown up, in effect you will see two different situations. What should be evident from the slide is that the dose that you actually pick to do your study and to study these two products is extremely critical if you're using this type of relationship to infer differences in dosage form performance, differences in release from the dosage form, and availability to the body.

We see at the top of the plateau where we're getting maximal effect, where we simply can give a lot more of the drug and we've maxed out the pharmacologic effect that we're going to get. You can have a very large difference between products. On this scale, since it's a log scale, you might see a ten times or one hundred times difference and see absolutely no difference in the therapeutic response. Obviously, if you went up to a big enough difference in dose, other effects perhaps unrelated to this might come into play, such as toxic effects. But in this effect that we're measuring, we see that we can have a very, very large difference in the performance of those products and see absolutely no difference in our clinical response.

If, however, we were to study it at a lower dose that was in this increasing part of the dose response curve, we would see a very nice difference in response with even a fairly small relative difference in dose between these two products. If we're going to do this, one of the problems is we have to have some idea of the dose response relationship. We have to do our study at a dose that is on that rising portion of the curve if we hope to be able to have that test show any existing difference. So that's critical and often we really don't know that. We don't

have a good idea of the correct and most sensitive dose range so it's very hard when we have to do this type of study to actually pick the dose that will give us sensitivity and actually tell us if there is a difference between the products. That's really critical and for that reason this doesn't have properties that are as easy to deal with as blood.

As you know from looking at clinical responses, either in patient treatment or in studies, the variability of these measurements is quite high for most clinical responses. In addition to the problem that I mentioned, that yields studies that are very large and often it's very easy to misjudge the power and not put enough patients in your trial. Therefore, you end up doing a large trial without any definitive results saying that the product is or is not bioequivalent. So this type of study, although it appears to be exactly what you want to see, is fraught with problems and actually ends up being fairly insensitive if not done perfectly.

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Again, this is a repeat of the straight plasma concentration curve. No matter what dose you pick, you still get the same relative response. A doubling of the dose would give a comparable increase in your outcome, which is plasma concentration, if you study it at a lower or a higher dose. That's a very nice property of plasma in addition to the fact that it has lower variability and needs fewer subjects to get at the same answer.

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The Regulations tell us that we have a number of options or approaches to determining bioequivalence and this regulation is cited on this slide and that is from 21 CFR 320.24. It gives us a list of approaches to determine bioequivalence in order of preference.

The first is an in vivo measure of active moiety or moieties in the biological fluid. That is at the top of the list for the reasons I just cited.

Other choices when that is not available or feasible are in-vivo pharmacodynamic comparisons. These are pharmacologic effects that hopefully can be quantitated and

studied in a controlled environment. They don't necessarily have to be done in patients but we look at an actual pharmacologic endpoint that can be quantitated. Sometimes there is no appropriate pharmacodynamic response available for that either.

Then we have to go to in vivo limited clinical comparisons. We use the same type of endpoints that were originally used to approve the product to begin with to prove safety or efficacy. We adapt that type of approach to do a comparative study. Obviously the study size, given the variability of clinical responses and the fact that often with the new drug products to begin with in order to show efficacy against a placebo you needed several thousand patients. Now we're trying to show differences or sameness between two products designed to perform in the same manner so that the need for patient numbers may go up considerably from the original trial.

If we can't do that, we have the option of doing valid in vitro comparisons. On this slide a couple of examples of each one are listed. Under in vitro comparisons, for example, we've done in vitro comparisons on cholestyramine, which is non-absorbable resin that binds bile salts in the GI track, to look at the ability of these different products to bind in an equivalent manner. In the laboratory in a very controlled manner investigators look at the ability of the two products to bind bile salts. They have to calculate all of the binding curve characteristics and those characteristics are compared in an equivalence fashion to make sure that the binding characteristics of these products are the same. That's an example of an in vitro comparison where we don't really study the bioequivalence in vivo because it would be extremely difficult to do that or at least it would be a trial that would probably involve the study of many, many thousands of patients; whereas, this gets at the function of these two products very efficiently.

The Regulations allow us to be creative if none of the above work and find other approaches that are appropriate and scientifically valid to show equivalence.

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The usual study designs that we do for bioequivalence are single-dose, two-way crossover fasted or fed studies. This

means that all of the test subjects receive both products. It is done in a crossover manner and products are given once to each subject on different occasions and then the bioequivalence and pharmacokinetic data and parameters are compared between the two treatments within each subject. Subjects serve as their own control.
We have alternatives to those studies when they are either not practical or not indicated.

Also, what has become another option is, instead of a regular two-way crossover, to give each subject the same product more than once. That's what we call a replicate design. It has some nice properties, although it means that each subject has to be in a four-arm study rather than a two-arm study. The overall number of subjects is less, but the number of times each subject has to come in is more. The advantage of that is it gives us an idea of within-subject variability whereas the two-way crossover simply gives you an idea of the between-subject variability as far as the comparison of these two products.

Also in certain cases we have to do multiple-dose two-way crossovers. This is often when we have to use patients in our trials if the drug is too toxic to be given to normal volunteers. Often the patients can't simply be studied in a single dose. They need the medication so we have to fit our study design into their normal treatment schedule.

Finally, clinical endpoint studies are often done with topicals or locally acting products. As I discussed before, we have no choice but to look at the normal clinical endpoints and do studies in patients because blood concentrations are not valid for those types of products.

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The Regulations allow us to not have to study every single strength of a product. For example, there are cases where we do a bioequivalence determination with full studies on a higher strength. The lower strengths of the test and reference products are proportional to their matching higher strengths and we do some in vitro testing to assure us that this is true. There is no reason to repeat the bioequivalence in vivo studies on every single strength. I think that's fairly well accepted in the scientific community as an efficient way to perform these studies. Often we grant waivers of those bioequivalence studies for

lower strengths and the criteria are listed in our regulations at 21 CFR 320.22.

For other types of products, such as topical solutions for the skin that don't have the transition from a solid state to a liquid state and are already in solution, we consider the bioequivalence to be self-evident since they really don't have anything in their formulation that could alter the bioavailability.

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The two parameters that we look at to determine bioequivalence that are derived from plasma concentrations are area under the plasma concentration time curve, or AUC, and maximum plasma concentration that's achieved after a dose, or Cmax. These are very simple pharmacokinetic parameters. You don't have to be an expert in pharmacokinetics to be able to figure them out. They are quite simple. They are not really overly dependent on any model or assumption. The AUC relates to the extent or how much drug is absorbed from a dosage form. Cmax is related to the rate. With a difference in rate, the maximum concentration or peak goes up or down so that it's sensitive to the rate of drug input from the formulation. You could conceivably have two formulations that would deliver the exact same amount of drug to the body but do it at very different rates. One could be fairly rapid with a high peak and one could take quite a bit longer with a lower peak. Those would not be considered equivalent if they were considerably different from each other.

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We assess these parameters by using 90% confidence intervals and these must fit between 80% and 125%. It's a misconception by most people, consumers and physicians alike, that we allow the mean of the data that we get from our studies to be as much as 80% below or 125% above. That's really not true. Because we're using these confidence intervals, the mean of the data never really gets close to these bounds. That's a very common misconception.

When we talk about the 80% and 125%, we're talking about confidence intervals and for those of us who are not statisticians, which is probably most of this audience, it is very difficult to figure out what we mean by confidence intervals. In effect, it's an expression of variability about the mean from a study so you might calculate a standard deviation or a coefficient of variation. If you know the number of patients or subjects in your study and you know that variability, the confidence interval calculations, whether they are 90% or 95%, are derived directly from those. It's yet another expression of variability of my data and how confident I am that I can extrapolate that small sample to determine what the true mean is in my entire population, which would be in all patients in this respect.

The confidence interval calculation on these relatively small studies yields a set of numbers with a width of the confidence interval. You have an upper bound and a lower bound for the confidence intervals and the mean sits in the center of those bounds. Therefore, the edge or either side of those confidence intervals is the area that can't exceed the 80% or 125%. This means that when the edge of the confidence interval reaches there and gets to one of these bounds, the mean of the data is still well inside the bounds.

You may have read in the medical literature that there can be as much as a
46% difference in generic products and the question is, can there be a 46% difference? When you really know how this works, it's actually kind of a ridiculous contention because the mean of the data never really gets close to that. When we have more or less failing studies, the mean of the data from our studies still isn't anywhere close to that. So 46% difference in the mean is just impossible.

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When we refer to a point estimate, we're really referring to the mean of the data from our study. The data is expressed as a relationship between the two products. When we talk about confidence intervals, we're talking about confidence intervals or means of the data expressed as T/R ratio, T being the data from the test and R being the data from the reference. The reference is usually the reference

listed drug or brand name product. The test is usually our potential generic product.

For example, a perfect relationship would be 1 or 100%. T/R would be exactly the same for whatever parameters we're looking at, AUC or Cmax. As T has greater bioavailability than R, we get up into the 100s and if the potential generic test product is less than the reference in its bioavailability parameter, it would be below 100%. Unfortunately, we have to use a little bit of statistics to explain this.

Using the bioequivalence criteria that I mentioned, there should be a few questions that come to everyone's mind when you first look at this. The first is an understanding that the mean isn't allowed to be as low as 80% or as high as 125%, but how do we come up with the 80% to 125%?

It seems a bit lopsided in that when you first look at it, we allow the 90% confidence interval of the test versus reference to be 25% above, in other words, the test is greater than the reference but on the other side we don't allow the 90% confidence interval to be less than 20% below (test is less than reference). What is the logic in that? It is based on actual statistical calculations that were done to this equivalence comparison. Most of the statistics that we've learned in courses and perhaps apply even to clinical studies are really attempting to show the difference between two or more things.

When one does a classical statistical test like a T test, you really come up with a conclusion that the two things are different or conversely, if you're unable to show that they're different, that you're unable to show that they're different. When you're unable to show that they're different, it doesn't mean that they're the same. It isn't a proof of sameness. It's simply that you failed to show they're different.

What we want, however, for bioequivalence is a statistically valid conclusion that the two things are the same within an acceptable range. The standard statistical approaches that we all know are not appropriate to get that conclusion. So some clever statisticians at the FDA came up with an adaption of the usual statistics to allow us to draw a conclusion of equivalence, not just an absence of difference.

The way they did this was called the one-sided test procedure. The approach simply is that two one-sided tests, very similar to T tests, are performed on this data. The first of the tests says that the test or T is not significantly less than the reference. The second test, that the reference is not significantly less than the test. So clinically, if I were to have a patient who goes into the pharmacy and is already on the brand name and the generic is substituted, I don't want the generic to be significantly less than what the patient is already on. Conversely, if the patient is on the generic and goes into the pharmacy and the reference is substituted for that product, I don't want that reference that the patient gets to be any less than what the patient is already on.

Those are the two tests that are done. Based on a lot of clinical experience and clinical input, the significant difference for statistical purposes was stated at 20%. That does not mean that the mean is allowed to be 20%. That's just the clinically significant difference that one sets for statistics. That's done statistically at an alpha level of 0.05 significance level for each of these tests. That's important, as I'll explain.

To express this mathematically, the T/R ratio of the first test, the maximum being 80/100, would be 80%. The second one, the R/T, also would be 80%. However, for a matter of convention, we express both of those in a comparable manner as T/R. We always speak of the test over reference. So R/T has to be converted to T/R by inverting it and it ends up having 100/80 or 125%.

It's merely that you'd have to take the reciprocal of the second one to end up with this somewhat odd-looking number, 125%. What this really translates into is that the test can't be 20% less than the reference statistically and the reference can't be 20% less than the test. Those are our two tests. That's why we often refer to it as 20% difference in either direction yet the confidence interval bounds don't seem to look like that.

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Here you see a picture of possible bioequivalence results. This is just an illustration of the types of results and it's meant to illustrate a couple of things. I have

displayed these with bars and you'll see a bar representing the width of the 90% confidence interval that we calculate. You have to remember that it's not an evenly distributed set of data. It's actually a bell-shaped curve where most of the data is in the middle around the mean and the incidence of data at the end tapers off. I've displayed it by bars because it's easier to look at.

The first one is hopefully a typical test versus reference comparison that we do on a generic product. As you'll see, the dark line in the center is the mean or point estimate of the data. The bars on either side are the width of the 90% confidence intervals. The reason we use 90% confidence intervals is because each of those tests is tested at the alpha = 0.05 level. So you have 0.05 or 5% on one side and 0.05 and 5% on the other side which represents the other side of the test. Therefore, what you're left with in the middle is 90%.

This is very nice. It's normal variability of the type of test that we see. The mean is depicted to be pretty much perfect. It's right on the ratio of 1 and the confidence intervals fit well within the 80 to 125% bound so this would be an acceptable product as far as a generic drug product. It passes and the mean or the center of the data is centered exactly where it should be.

However, if one has a slightly less variability, in other words, we have more certainty of the response or relationship, the confidence interval limit bounds allow it to be slightly off-center. So the second one again shows a passing study; however, the point estimate or mean of the data from the study is, in this case, less than 1. So it may be 90% or 92%, something like that. Yet, because of the low variability, the confidence interval bounds still fit within our acceptance criteria. The lower the variability, the more the system allows the mean of the data to be off-center, although this is not an effect that will allow anything to pass as you'll see.
The third one is kind of an extreme example. We would never see it because no one would submit it to us. This is a study where, even though the mean or the point estimate or center of the data is perfect, right on a ratio of 1, the variability and confidence intervals of this product, and it could be variability of the product or inherent variability of the drug itself in the pharmacokinetics, are so wide that it fails on both sides. It's simply

unacceptable even though the center of the data is exactly where it should be. One can see if you have high variability or a lot of uncertainty in this relationship, it would fail as well and would be an unacceptable product.

The next one shows a product where it's kind of a close call, but it does fail. This study would not support the approval of a generic drug product. Even though the mean or point estimate is well within bounds, the upper bound of the 90% confidence interval goes over our goal post or range and is probably 126% or so. Therefore, this is a failure of a study. If this were the only study we had to look at, we would not approve this as a generic product.

One of the things that affects this confidence interval is the number of subjects you use in your study. If a firm had this type of result and this was a true depiction of how their drug product performed, they could probably go back and do a lot larger study and maybe this might pass the next time around. It's not a product that's so different from the reference that it would be guaranteed to fail every time. Sometimes doing a better or more appropriately powered study might have a chance of passing. Then again, it might not.

The next one is even worse in that even the point estimate or mean is over the edge. It is possible but very unlikely that you could do anything to save this product. Doing another study wouldn't be helpful at all. If the mean is over, chances are that just increasing the power probably wouldn't help you.

The last one depicts a product that is totally outside of the confidence interval bounds. It's very, very different. In no respect would this be ever considered equivalent. In fact, there are some people out there who informally call a result like this inequivalent, proof that these products are definitely not equivalent and never will be. A company that gets this should just go back and totally redo the product because there is absolutely no way that this product would ever be considered equivalent or same or therapeutically equivalent.

These tests are actually quite strict and control most drug products quite well. There's a lot of belief out there that's not correct, that this is some kind of liberal system that allows any types of products to get through and

that nothing ever fails. This is something that is not true. This is actually quite a stringent test of products. Perhaps it could be argued that it might be too strict for a lot of products.

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One of the things that people continually have great concern over is what's termed now as Narrow Therapeutic Index Drugs (NTIs). These are fortunately a relatively small number of drugs where the dose or therapeutic concentration of drug that must be given to obtain the therapeutic effect is very, very close to the dose that gives serious toxic effects. There's not really much room for error on these. That's why they're carefully monitored using both clinical and plasma concentration monitoring.

There is a lot of concern with generics of these products. The concern is that, if the generic product gives a clinically significant higher dose than the reference product, we will see toxicity that we wouldn't see with the brand name product, even at the exact same dose. Some examples of these products are digoxin, lithium, phenytoin, and warfarin of which all have generics.

There was considerable controversy surrounding these products. A lot of it was from the innovator companies but there were also many concerned clinicians who were honestly concerned about the welfare of their patients and whether we were doing the right thing in assessing NTI drugs correctly. We haven't found it necessary to alter the bioequivalence limits simply because they're quite strict to begin with. We are constantly assessing the adequacy of these limits for these products and other products and so far, at least for the NTI products we've looked at, we don't believe based on our scientific assessment that there's any need to change or tighten up these limits. However, we are constantly looking at those things and assessing data as it comes in and we will act accordingly should the overall data actually support the need for decreasing those confidence interval goalposts for a given NTI product.

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This concludes our overview of the generics drug approval process. Thank you.