

Medpace Bioanalytical in Drug Development

DR. YONG-XI LI: Today, the title of my talk is Medpace Bioanalytical in Drug Development.

What is Special About the Bioanalytical Lab vs. Other Testing Labs?

First we want to see what is the difference between bioanalytical laboratories and other testing laboratories. For example, environment: testing laboratories or even reference laboratories, and central laboratories may be different. Because in these other laboratories, the method is well established. Therefore in every laboratory all over the world, no matter what kind of laboratories they use, they can follow the existing methods to analyze something. As an example, cholesterol, glucose, other diagnostics or environmental testing, environmental monitoring, everybody can follow the same procedures to do that work. Even in different environments, different cities, different laboratories, the work can be identical.

However, for bioanalytical laboratories, they're dealing with biological samples of the analytes of interest. What is the interest? Analytes, drugs, pro-drugs, drug's metabolites or, sometimes, biomarkers. All of these drugs or metabolites are unknown until you analyze the sample. After you analyze the sample, you know the structure of this drug or the structure of the metabolites.

Therefore, in the bioanalytical laboratory, you're dealing with an unknown method. So you have to develop it yourself. Different laboratories, for instance, may develop a method totally different from our bioanalytical laboratory. Therefore, you cannot use this method in that bioanalytical laboratory. And their method cannot come here. So the FDA requests that if you develop anything, you have to validate the method to prove the method is reliable and accurate. You also have to validate that any process during sample handling

does not change the sample. For instance, if you are handling your sample during extraction, if you are receiving the samples, putting them in the freezer, and taking samples out from the freezer, you need to be certain the samples are put in the freezer on the top. You have to prove that, during all of these processes, the method used didn't change the samples. We call that validation. You cannot do validation by your own opinion. You have to follow US FDA or OECD guidance to do the validation.



Dr. Yong-Xi Li

Executive Director of the Medpace Bioanalytical Laboratories

Dr. Li has a strong background in bioanalytical technology, method development, validation, and sample analysis in support of pharmaceutical development and both preclinical and clinical studies.

For more information on Dr. Li, see page 7.

Bioanalytical Lab: Science and Regulatory

So there are two things that are totally different from other testing laboratories. One is having to do the development work yourself. Secondly, is having to validate the method by yourself and to prove to the regulatory agency your method is reliable. And also for the bioanalytical method, in drugs, metabolites, that deal with human life, and deal with animal life, you have to very carefully develop a method that is sensitive enough to detect at a very low level the analytes: the drugs, the drug metabolites, or sometimes the biomarker. This is a totally different concept from other testing laboratories.

The Drug Development Process

We look at the drug development process. From the beginning we call it the discovery stage. You may have 10,000 compounds. It doesn't matter if they're from combinatorial chemistry, from your company synthesis laboratory, from natural products, or from your database. If you choose 10,000 compounds for your target, then only 2.5% can pass through to go to the preclinical stage. In preclinical, they are all used for animal testing, for rats, mice, dogs, or monkeys. All of these tests, as Dr. Wei said, are for dosing range levels, Tox or PK, for whatever you are testing. Another 2% pass through to the clinical phase. So the numbers may go from 10,000 compounds to 250 to 5 compounds.

After all the phases – Phase I, Phase II, Phase III studies – you may go to the FDA and then receive approval for maybe only one compound. So from here you can see, even as we look at 10,000 compounds, you have to develop 10,000 methods because of different compounds. Of course we can talk about the methods being “dirty”, quick method developments. We can use two or four hours to develop the method and then go to analyze the samples. Usually there are six rats for dosing your drug and you receive 8 time points for each rat, so you have a total of 48 samples. One method with 48 samples for determining this compound, can go down or not. So from here, during one drug development process, to get a successful FDA approval, you have to develop 17,500 methods. Among them, 755 methods you will have to validate under the FDA guidance.

And as a total we have to analyze 500,000 samples just for one drug. You can see huge amount. And also from here you see the failure rate is very high from 10,000 to one or two compounds.

In Vitro ADMET

And why failure? Basically it's bioanalytical which can determine more than 50% or 60% due to ADMET: Absorption, Distribution, Metabolism, Excretion, and Tox. All these are bioanalytical determinations of the fate of the drug. If failed, the compound is done, withdrawn.

Agency (FDA) Perspective on Pharmacokinetic Analysis

To have a compound go to NDA submission, Dr. Brian Booth reviewed 27 NDA submissions. Among the submissions, five of the submissions had a bioanalytical issue problem. For bioanalytical, you have to be careful because it's very costly. The science is very important. Regulatory is also very important.

How expensive is this process? How long will it take from your leading compound, to lead selection, to go to the developmental stage? We found a new chemical entity and then to get to one product. How much? 12 years and 900 to 1,000 million dollars. This is why our health insurance is so expensive - for the development of one drug we spend so much money and time. In the past 12 years, bioanalytical work occupies 30% to 35% of time. And total capital is around 30% of capital investment just for bioanalytical work.

Bioanalytical Changes Over 15 Years

How can we reduce this time? Reduce the money? Everybody discusses: high through-put along with different things. We need to increase the through-put and then reduce the time, reduce the money. What can bioanalytical do? I think it is the LC-MS/MS system that can make the difference. It's not immuno assay; it's not HPLC assay; it's not GC assay. We can look at the actual numbers over the past 15 years, and the samples analyzed by LC-MS/MS assay have significantly increased.

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But there are other methods: for HPLC, for immuno assay, RIA method or ELISA method, decrease. So naturally for bioanalytical laboratories you have to concentrate on MassSpec. Separately from the scientist, the instrumentation, and the regulatory agencies.

Multi Reaction Monitoring

What is MassSpec? It is like three ordinary MassSpec put together – one, two, three – Q1, Q2, Q3. Three conventional Mass Spectrometers put together. And then if we have different combinations of these three, they give you different functions. For example, if we shut off Q3, Q2, only leave Q1 on, or shut off Q1 and Q2 and only leave Q3 on, we can determine the molecule weight of a drug or the molecule weight of metabolite. If we select Q1 on, for instance, and only allow one drug 500 molecule weight to pass through here, break it and Q3 scan it to get fragments. In that case we can, from fragments, come back to figure out your drug structure.

And also we can do what we call the neutral loss. If these two, Q1 and Q3, both scans, keep synchronized with a different mass, for instance 89 or whatever numbers different or certain amount synchronized. For instance, this (Q1) scans 100, this (Q3) is scanning 189. Then if this (Q1) scans 200. This (Q3) scans 289 etc. In that case we can find out, for instance, in proteomics, phosphorylation, and your protein how to change. You can scan the same thing.

You can see this is very, very powerful instrumentation or bioanalytical tools. Here the most important thing is quantitation. We call it MRM mode. It's Multiple Reaction Monitoring. What is this doing?

After HPLC Separation of Drug

It is very difficult to see here, but I will use the next slide to show you. After HPLC separation of drug and metabolites, ionizing it. Q1 only allows, for instance, a

drug, here is Hyoscyamine, I only allow Hyoscyamine passing through. The rest of them, metabolites or impurities or whatever. endogenous compounds, I'm sorry you cannot pass through. You're hitting the quadruple, go to the ground. And then at Q2 we break it. And then at Q3 we only monitor one piece of your fragments, that we call characteristic function group.

So therefore, giving you the definition for your drug is number one, your molecule weight must meet my requirement. Second, your structure information must meet my requirement. Therefore, you can quantify your compounds. And then if you have metabolite one (M1), metabolites two (M2), for instance hydroxy metabolite, this methyl group replaced by hydroxyl group. Okay I determine this hydroxy metabolite one, and break it, determine hydroxy piece of fragments. And continue go to M2 (metabolite 2). So one, two, three. One, two, three. One, two, three (instrument does). Always in this way we can determine how many metabolites, and how many drugs, we can do it. There are not any other tools that can do it this way.

So as a result, because you only allow Hyoscyamine to pass through, the background from here, decreases. And later on, you only allow this fragment to pass through. So the baseline will continue to decrease. Therefore the signal to noise ratio is significantly improved. This is why LC-MS/MS can determine very low level of the analyte.

The reason is, the background is very low. So if your signal is here, like the original situation signal half way, you cannot see it because the signal disappears into the background. Because MRM mode significantly decreases the background, the peak intensities are very high. Even if you cut it in half, there is no problem you can detect.

There is also another advantage I just mentioned: if your drug and drug metabolites are M1, M2, and you do one, two, three, one, two, three, you still can separate and quantify the three compounds (even they

overlap together). For HPLC you have to separate them. For immuno assay, RIA, and ELISA, there is no way to do mixture. So this is why LC-MS/MS are very unique tools for bioanalytical testing. As a result, no other detection methods can reach the level and have such a fast turn-around like LC-MS/MS. This is why we can speed up and reduce the developing years. Reduce the cost of the developing process. The specificities are very high. That means the data integrity is very great.

Lead Selections

And as a bioanalytical laboratory, we also do lead selections at the discovery stage, preclinical stage, and clinical stage. Dr. Wei just gave a great talk for earlier clinical studies, Phase I, Phase IIa. But here we also are dealing with not only late phase analysis but preclinical analysis and also discovery stage. For discoveries, the challenge is high salt. The reason is phosphate buffer, but for preclinical animal studies is a high protein or different enzymes, for instance, rat and mouse are different from pig, from dog, different from monkey, and also different from human.

And sometimes... we did one project for woodchuck. Maybe people are surprised at the woodchuck. I tell you the woodchuck is a very great animal model for Hepatitis C. If you want to develop a Hepatitis C drug the woodchuck is the best. So in your yard, if you have a woodchuck, please keep it for animal studies. And then we have humans. Everybody knows humans have interferences, because people's habits are different. You are different. Mary is different. Mary likes chocolate. I do not like it. Or Rob maybe likes to smoke. I do not know if you smoke or not. But just different habits. You cannot put humans into a cage like in animal studies. You cannot do that.

Therefore, you do not know what's going on. Then in the human, there are so many interferences. This is why in bioanalytical you're dealing with different challenges.

Everybody knows humans have interferences, because people's habits are different. You are different. Mary is different. Mary likes chocolate. I do not like it. Or Rob maybe likes to smoke. I do not know if you smoke or not. But just different habits. You cannot put humans into a cage like in animal studies.

Medpace Bioanalytical Laboratories (MBL) and Methods

Okay Medpace. Based on this kind of concept, in Medpace Bioanalytical Laboratories, we chose our people very carefully. All people, and our study directors have PhD degrees or Master degrees. They also have an average of 12 to 15 years in the bioanalytical area. And I'm talking about experience including science and including regulatory. This is our beautiful team. And also we have big support system, big support. We have former FDA officers, like Dr. Jim Wei who is an immediate senior reviewer. We also have others. Dr. Troendle himself is also a former FDA officer. We have an onsite QA unit. Every two weeks they have meetings with us. And then most importantly we have a validated Watson LIMS system with a very great PK package. We are validated. All this can support our data integrity. This slide is a validation book bundles.

In Medpace Bioanalytical Laboratories, we chose our people very carefully. All people, and our study directors have PhD degrees or Master degrees. They also have an average of 12 to 15 years in the bioanalytical area.

And another important thing we have: top-line instruments. That is API-5500 Q Trap system which is, so far, the most sensitive instrument in the world. We have two of these pieces of equipment. We also have a very precise sample automation work station. We have two here. So every day we can precisely analyze, based on our capability now, at least 2,000 to 3,000 samples.

What Does the Agency Worry About (with Analytical Methods)?

I will now talk about our method. Many people think we talk about matrix effect, ion suppression, endogenous, interference, etc. These issues are what everybody talks about. But today I want to talk about the methods development in the MBL is based on FDA officer's opinion. What are the agency worries about bioanalytical laboratories? They worry about the following issues: the first is, you didn't detect the correct compounds. The second is, you have interferences. Your calibration and QC samples are not right. The third is, sensitivity is not high enough to determine the disposition of the drug. The fourth is, they worry about your method reproducibility. This one is easy to talk about. In 2007 in the Crystal meeting, even before it was a guidance, they emphasize that you have to analyze 10% of incurred sample re-analysis. What does that mean? For instance Dr. Wei did a clinical trial. There were 1,000 samples. We analyzed 1,000 samples. We got the data. But if you use more than 10% of those samples, after your

study is finished, you have to re-analyze again using your method. Compare the re-analyzed data with the original data. You have to compare. If it failed, you cannot submit that data. Even if there's no guidance from 2007 until today, if you look at the FDA website, they issued 483 letters. So, many different bioanalytical laboratories, because they didn't do that, and they have no guidance yet.

So there, you have to be careful. I do not talk about this anymore. I will talk about this during part three. We face the challenge. How did we overcome the difficulties? To share this experience; share these challenges with our people, audience and clients here.

What Happens if the Correct Compound was Not Measured?

First, what happens if the correct compound is not measured? The FDA examined one study. They found this curve. How come it's different from others? Suspect is this free drug? And later on we checked out our data. Indeed we found out at the low end, it is

out of acceptance criteria. And we check the actual situation from science.

Sulfur Atoms

This compound – I'm sorry I cannot draw the structure because this is a client's compound. So I only can draw a square here. But I want to talk about the sulfur atoms here. This is five member ring. Nearby is cation of nitrogen. So cations of nitrogen have hydrogen transfer, therefore, this ring is easy to open. The opened sulfur atom was replaced by two oxygen atoms. If nominal atomic weight for sulfur is 32, two oxygen (atoms) is also 32. So therefore molecule weight are all 490. On ordinary, conventional MRM on the MassSpec, there is no way to distinguish those two. So the only way is to try to separate those two. However they're so close to each other. Even if you do your best, spend a lot of time, maybe still overlap easily. You can see some bump there but you still cannot separate. So our scientist is very smart.

We do not want to spend energy. So you have a bump. Okay a bump. And then I use high resolution because we have API-5500 Q Trap. We use high resolution. That makes peak is not one molecule weight (AMU width). We used 0.1 or 0.08 AMU, high resolution to do it. Finally we get a success. This is why from high resolution MRM quantitation, we get

rid of interference of these. So finally we get a correct number for all these studies.

Another Example for Wrong Chemical Species/Entity Measured

Another example for wrong chemical entity measurement was recently found when we did a Cyclophosphamide. This compound from here, it's pharmacokinetic. We can see this drug is easily metabolized and becomes Hydroxy metabolite in the human plasma. This is an active metabolite. Actually it continues to metabolize in kidney and we get a Phosphoramidate mustard. This is alkylating agent. It kills cancer cells. But the trouble is they also have a stable Keto- metabolite. This hydroxyl group became keto- group. There are two mass units of difference. One is 275, one is 277. In an ordinary situation, MassSpec can distinguish these two AMU counts without any problem. The trouble is these two chlorine. These two chlorine give me trouble. That is because two chlorine have M+2 isotope peaks. Therefore for this compound, at 277, they have 279 isotope. For this, they had 275, they have 277 isotope. There's common ions 277... 277 here. So if you use 277 to determine for hydroxycyclophosphamide it's like this. We get one beautiful peak here but a very ugly peak here. But all people like beautiful peaks. The beautiful peaks here are this. Indeed based on this, we did the calibrating curve very linear, very beautiful linearity. So we did a lot of work based on this peak. Actually it is wrong, the smart scientist Dr. Lu is sitting there; he found this ugly peak, so it should be right. That gave us trouble. That was before we did something wrong. This ugly peak has another problem. Another big problem of this ugly peak is that it is changeable. All the time, they change. Sometimes it's high. Sometimes it's low. Sometimes it disappears. So this is a very big problem.

Later on, we have another smart guy. He developed a method using high resolution with the API-5500 Q Trap. We use high resolution and he also found a way to stop this active metabolite continuing to change. So this method is now in our laboratory completely validated. Right now we continue to do our best, try to get another simple method to be validated. So this is how important it is to correctly identify the compound in the bioanalytical laboratory. We face so many challenges.

In this case you can guarantee your drug disposition at least 97%. This is why you need to go to a very low sensitivity of detection. This is our strength.

And next, the agency pays attention to QC samples, calibration standards. This is one of our ANDA submissions. It's a generic drug. Not long after we submit this ANDA submission, the FDA gave out a very long letter asking us to provide bioequivalence deficiencies to the applicant. You have to be careful. And then there is one question. Please submit mean precision and accuracy data for standard and QCs. We said, hey, we did. This is very important, common knowledge that everybody provides. Why do they still ask this question? Finally we understand. We told the

FDA officer we understand. The reason is our calibration range was not so right. This is from 5 pg/mL to 1500 pg/mL. Only 300 fold. We think it's narrow enough but, however, finally sample concentrations are all here. Did you see the blue dots? All concentrations are nearby (to low end). This happened due to some clients. They always want to ask to go to very low and low detection. And also need the calibration range very, very high.

In this case they need not do re-analysis if over the calibration curve. They can save money. But in fact this give you big trouble. Because for generic drugs, the only thing the FDA looks at is PK. But you get PK is 125%. Is it true or not? This is questionable. Because here the calibration range, you go this, go that, will affect these data.

So finally, and also this is a big issue for generic drug submission. Because whomever is first approved by the FDA will have half a year on the market alone. If you and other people submitted these generic applications, sorry, half a year later. So if somebody gets passed, you have half year on the market. It is big money. So in this time we submit this one, we get big issue and client asked us to re-do it. They don't want to get FDA letters for a second time. So we reduce the calibration range from 5 to 150 pg/mL— 30 fold — and then we get concentrations are here. Luckily accurate analysis we go the PK of 119%. Passed. Everybody happy.

Sensitivity: Enough to Assess the Disposition of the Drug?

And the last question the FDA pays attention to is sensitivity. What is sensitivity? This is not my drawing, it is FDA officer drawing. I just copy it. Because you have to provide at least 5 times of $T_{1/2}$. That means half life. In this case you can guarantee your drug disposition at least 97%. This is why you need to go to a very low sensitivity of detection. This is our strength. I can proudly say the Medpace Bioanalytical

Laboratories have very good experiences; we can get very sensitive methods. I give one example.

For Small Molecule Drugs

We use one typical example for a small molecule drug. This is Capecitabine. It has three active metabolites, including 5-FU. 5-FU itself is also one drug – oncology drug. 5-FU is a very small molecule. The molecule weight is only about 128. Therefore, there is a lot of high background, high interference. The background is almost 4,000. More than 4,000 you can see the baseline. And also, in the interference, you can see a bump. Obviously there is a bump there for this kind of compound. This method has many challenges for a bioanalytical laboratory. They try to clean up the sample. Use different SPE to clean. Clean this way, clean that way. And then finally use very difficult chromatography conditions to separate all these interference. We think that is not a good way. It does not save money this way. Again, our scientists are very smart. We just use this kind of equipment (API-5500 Q Trap) and also use high resolution MRM. That means: here is one mass unit. But for us we only use 0.1 mass unit (AMU) and use high resolution. Of course sensitivity is much lower. This reaches 12,000, but here only 4,000. But you can look at the background. It decreased from 4,000 to 100. So signal to noise ratio increased. Very easy to detect 1 ng/mL.

High Resolution with High Scan Speed vs. Unit Resolution with Regular Scan Speed on AP-5500 Q Trap

Another thing is, in the plasma you have interference peaks. If I use it, I do not use a chromatogram to separate that use. It is too much time, and too much money. I just use high resolution. You can see this peak because the peak is much narrower so the interference is separated. Great. So for us to go down to 0.1 ng/mL of LLOQ for 5-FU is no problem. So far this is the most sensitive method for 5-FU in the world. I can say this. And of course I do propaganda for Dr. Bill Heckle here. This is a good instrument, contribution, API-5500 Q Trap's function.

Unique Feature of API-5500 Q Trap

Why can we do this? Because this new instrument API-5500 Q Trap, it has very high frequency – 1.228 megahertz. Conventional API-4000 only has 800 kilohertz. Therefore, when you do this peak, for in-

stance, this peak is a very narrow peak; we only have one, two, three, four, five, six, seven digital points to construct this peak. If you use conventional speed it's 100 milliseconds. Dwell time. Here it will total seven points times 5 (ms Dwell time) we only have 35 milliseconds total. If you use 100 milliseconds your first point is here and your second point is here. That means that narrow peak disappears. Did you follow what I'm saying? So for 100 milliseconds you cannot do this kind of high resolution. The only way to do it, your Dwell time much shorter, five millisecond. I was told this instrument can go down to two millisecond. But we use 5 ms to get seven points, we can construct a peak very nicely. This is why we can determine very low limit of concentrations. We need not struggle with the method, separation, clean up of the sample, etc. Sorry I'm lazy but I use my high technology. The cost is much better.

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For Large Molecule Drugs

And another example for sensitivity is for large molecule drug which is Exenatide. Exenatide is like this. Okay if you look at a structure even I cannot recognize what they are. I'm too lazy to read all this carbon, hydrogen, oxygen, or whatever. But anyway this is a very large molecule. It's 39 amino acids. Okay? Molecule weight is about 4,000. If you go to a very low level, for instance, 1 ng/mL, not so many molecules in it, how can you detect? So this is a very big challenge. One of our clients called me and wrote me an e-mail. She said, Dear Yong-Xi. My name is Yong-Xi. But anyway, they said they run into some difficulties with the assay. They actually used a different bioanalytical laboratory. They finally have no way to develop the method. Ask me whether I can do the method and look for LLOQ of 1 ng/mL.

Fast and Selective MS/MS/MS Quantitation

So finally again we do not think conventional, ordinary bioanalytical way can do it. Again, our smart scientists make decision we go to try, we call it MS3 quantitation. What is MS3? This is your analyzer, for instance, Exenatide, you can pass through Q1. We can only let him pass through. The rest of them are blocked here. This passed through; Exenatide passes to here. We break, it becomes the daughter. This piece, all the rest of the daughter, rest of the fragment, I'm sorry do not let you go, only this small piece daughter passes through again. It reaches here, this is linear ion trap. If they come to here. We fragment this daughter again and it becomes grand-daughter – daughter's daughter – granddaughter. We

choose this. That means we identify Exenatide which must have three conditions. First, molecule weight must be right. Second, the daughter must be right. Third, the granddaughter must be right. So three factors give you definition of Exenatide. So very specific. Therefore we get it like this.

Q1 Scan, Product Scan, and Daughter's Daughter Scan for Exenatide

We did parent 838 and then first daughter is 396, 397 and the granddaughter from 397 go down to 202. So we use 838, 397, and 202 to determine Exenatide. All again this is a smart gentleman who did this method.

LLOQ & ULOQ of the Method for Exenatide

So finally we can get 5 ng/mL. It is so beautiful. Totally not any background. Of course our high end is 2,000 ng/mL, so we get calibration curve from 5 to 2,000 ng/mL. You can see so beautiful linearity for so large molecule. I cannot believe it. By the way compared with this gentleman's company. They did in their machine. They're manufacture company. They much more understand the instrument than us. But they did it from 250 to 1,000, only four-fold, it still got quadratic calibration curve. Plus their low limit of quantitation is only 250. We are so great from 5 to 2,000, which is good. So we're proud of this thing.

Selected Methods Validated at MBL

Of course every sensitivity is correctly identified. Our laboratory, during this half year, validated so many methods. These are diabetes drugs – Metformin, Glipizide, Actoz. And also this one is a cholesterol reducing drug and all these, Clopidogral, all of these are anti-clog drugs, for heart disease, for blood system disease. And these are all oncology drugs.

But here you have antibiotic drugs. Most importantly I want to emphasize we have very good vitamin D and vitamin A methods. This vitamin D we did was very successful. Vitamin A is in the process. We validated methods so great in the validation process. So all these large molecules – we have Exenatide, Leuprolide, Octreotide, Thymosin, and Insulin. Today one of our visitors asked us whether we can do testosterone. Luckily we validated testosterone method. Including testosterone metabolite Dihydro-testosterone. We totally validated the method under the GLP conditions. Of course Medpace is more than happy to partner with new or existing clients to develop non-proprietary methods.

If you have any needs just call us or e-mail us. We can do this for you. We can cut your expenses. We can speed up your clinical or preclinical study design. We are waiting to do that.

What is special about MBL?

So finally my talk is finished. We bring so many benefits to our clients. You're also welcome, everybody, to visit our beautiful laboratories and if you have any comments or questions you're welcome. Thank you for your attention.

About the Presenter

At Medpace, Dr. Li directs operations and activities of the advanced Mass Spectrometry Medpace Bioanalytical Laboratories, including bioanalytical aspects for small and large drug molecules according to GLP and GMP compliances and ICH guidelines. He has authored numerous scientific and clinical publications in the fields of proteomics and quantitation analysis.

Medpace Bioanalytical Laboratories

4750 Forest Avenue, Suite Q
Cincinnati, Ohio 45212
USA

Toll-free: +1.866.902.9125
Tel: +1.513.366.3260
Fax: +1.513.366.3261
E-mail: info.mbl@medpace.com

Medpace, Inc.

4620 Wesley Avenue
Cincinnati, Ohio 45212
USA

Toll-free: +1.800.730.5779
Tel: +1.513.579.9911
Fax: +1.513.579.0444
E-mail: info@medpace.com

Medpace can do this for you. We can cut your expenses. We can speed up your clinical or preclinical study design. We are waiting to do that.