

# CLOSERLOOK

## MEMORANDUM

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### Interview with Dr. David Orloff – January 21, 2009

Close Concerns recently had the distinct honor of discussing the recent FDA cardiovascular risk assessment guidelines for diabetes drugs with Dr. David Orloff, the former director of the division of metabolism and endocrinology products at FDA, and currently executive director of regulatory affairs at Medpace, Inc. As a reminder, companies who receive the letter must show that their drug does not increase cardiovascular risk by performing a meta-analysis of important cardiovascular events across phase 2 and 3 controlled clinical trials. The upper bound of the 2-sided 95% confidence interval for the estimated risk ratio of cardiovascular events in the intervention group vs. control group should be less than 1.8. If the aforementioned meta-analyses fail to meet this upper bounds, a large safety trial should be conducted that alone, or with other trials, do satisfy this upper bound. We discussed with Dr. Orloff the details and implications of this requirement as we are very concerned that these new requirements will slow down drug development and stifle innovation.

In our discussion with Dr. Orloff, he pointed out that it would increase the cost and time of developing a diabetes drug, but he felt that the “silver lining” would be a greater level of assuredness about the safety profile of the drug. While we believe this could be the emergence of cardioprotective drugs for best in class therapies, of course that would have to be proven in trials over many years, and that may ultimately be very hard to demonstrate because the drugs will be measured against patients on standards of care to modify the known cardiovascular risk factors, notably lipids and blood pressure. In the meantime, from a patient perspective, we point out that no one ever measures the cost to patients who are not treated by a therapy that could have been. The guidance came at a difficult moment, economically speaking, particularly for small companies who are unable to raise funds in the current capital-constrained environment. Dr. Orloff said that there would likely be several companies that discontinued development of their diabetes drugs, but he hoped that the best candidates would rise to the top and continue on with their development. We hope that the FDA will be able to find a middle ground where they are assuring that safe and efficacious drugs make it to market in a timely manner.

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### FDA GUIDELINES ON CARDIOVASCULAR RISK ASSESSMENT

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**MELISSA TJOTA:** Could we discuss the contents of the letter that FDA sent companies with diabetes drugs in development – we would welcome your characterization and view.

**DR. DAVID ORLOFF:** I’m assuming the details of the requirement are known to you and your readers. Beyond setting down the basic evidence requirements, what the letter says, in effect, is “We encourage you to come in and talk to us about what your plans are going to be.” That is not a disingenuous statement. They don’t know yet how to accomplish this exclusion-of-risk exercise, at least they don’t have a single prescribed approach, so it is open to discussion, and it seems they are intent on giving input to sponsors. I suppose you could say they know their destination, but they haven’t figured out exactly what the route is. That is one important thing. The second thing is that the approach to the problem of ruling out CV risk will differ depending upon where a drug is in development. The company that is just coming up to phase two has a prospective plan to make which will conceivably have a major impact on the design of the phase 2 and phase 3 program. A company that is finishing phase three will have to

undertake a retrospective analysis and potentially supplement their development program with additional studies either pre- or post-approval in order to provide the necessary assurance of CV safety.

**KELLY CLOSE:** What about generics – how are they affected?

**DR. ORLOFF:** Generics get approved based upon pharmaceutical equivalence and bioequivalence, so remember that demonstration of efficacy and safety for a generic is not required, since that information has been established for the reference product of which the generic is deemed a therapeutic equivalent.

**MELISSA:** Can you give us your view on how reasonable the requirements are for the meta-analysis?

**DR. ORLOFF:** I gather you are asking about how “doable” this requirement is. The FDA has asked that data be presented to permit the conclusion at the time of initial approval that if your drug increases CV risk at all, that increase is not more than 80%. Specifically, based on CV events like MI, cardiovascular death, and stroke observed across clinical studies, they want 95% “confidence” that whatever the ratio of risk of the new drug relative to the comparator (either placebo or active), it is not *greater than* 1.8. Additionally, the FDA has also stated that an observed risk ratio for CV events of 1.5 (i.e., a 50% increase in risk with the new drug) would likely preclude approval, regardless of the upper bound of the 95% confidence interval for the risk ratio. So they have defined “unacceptable” potential harm based on a standard for both the observed risk ratio and the 95% confidence interval for the ratio.

Now in order to accomplish this demonstration of absence of an “unacceptable” degree of CV harm, patients in the clinical studies will need to experience some minimum number of “hard” CV events during the period of follow up. Whether in a single dedicated CV outcomes study or across a pool of smaller studies, this number has been estimated to be in the range of 130-150 events. Assuming an observed risk ratio well below 1.5, this would permit the exclusion, at the upper bound of the 95% confidence interval, of a risk ratio of 1.8. Assuming that neither study drug nor placebo has any effect, positive or negative, on CV risk, then the total number of events will accrue as the “natural history” of the patients’ underlying cardiovascular disease “plays” out. It is then the magnitude of the risk (e.g., in percent per year) in the overall population that will determine how many patients need to be followed for how long in order to tally the necessary number of events. For example, in a patient population with a 2% per year (two patients per 100 per year) risk for a CV event, it would require 15,000 patients followed for one year, of 7,500 followed for two years, or 5,000 followed for three years, and so on, to garner approximately 150 events.

The FDA has suggested that the necessary events could come from the pool of phase 2 and 3 studies designed to explore the glucose-lowering efficacy and general safety of the drug. If these studies did not yield sufficient events, the total could be supplemented by the events accrued in an appropriately designed dedicated CV safety study. Is this “doable?” Certainly. Is it a walk in the park? Absolutely not. There are methodologic requirements and complexities that have not traditionally characterized pre-approval diabetes programs, but the investigative field is very comfortable in the design and implementation of studies examining effects of therapeutic interventions on hard CV outcomes. Whether pooling across studies or a single dedicated trial, the fundamental approach to analysis of event rates and comparisons across treatment groups will be similar and nothing new. The “challenge” then is this: to enroll and follow for sufficient periods the study population(s) at sufficiently high risk for CV events that the question of risk associated with drug can be answered in a reasonable period and at an acceptable cost.

**KELLY:** What are some of the methodologic complexities of this new requirement?

**DR. ORLOFF:** Some companies will be facing this standard at the beginning of a development program and can plan accordingly, in terms of overall program design, study objectives, population CV risk, plans for pooling, timely initiation of dedicated outcomes studies. Other companies will be hearing of this requirement at a point well along in drug development, perhaps even as they complete phase 3. For the former companies, I’d say that a major issue is whether high CV risk patients (with previous CV history, multiple risk factors, renal insufficiency, and potentially complex medical as well as antidiabetic regimens) will be amenable to study in traditional glucose lowering clinical

trials that have formed the basis for labeling of diabetes drugs for many years. These companies will need to rethink the glucose-lowering portion of their development program, along with FDA, perhaps deciding that a more limited set of glucose lowering studies in the usual generally healthy diabetic populations will suffice to support labeling regarding dosing and glucose lowering effects. In these cases, sponsor would likely plan for a dedicated CV safety study which would provide not only the necessary CV events to exclude “unacceptable” risk but also would provide the long-term exposures necessary to characterize the overall safety and tolerability of the new drug in the target population. For sponsors already well along in their programs, if they do not have sufficient events to exclude “unacceptable” CV risk, then they will have to discuss with FDA the necessity and timing of submission of data from a dedicated CV safety study.

**MELISSA:** Instituting a Guidance for Industry without first publishing a Draft Guidance and collecting public comment is unusual. Why do you think FDA took this step now?

**DR. ORLOFF:** From a patient perspective, this is discomfiting, especially because the FDA purports to integrate the patient view. We so appreciate patient representative Rebecca Killion's contributions and were surprised and disappointed not to have had a chance to offer comment. A guidance still simply represents the FDA's best current thinking on an issue. Even if the issue of CV risk exclusion per se is not open for discussion, the FDA does expect and intend to confer with sponsors on the approach to accomplishing it. Whether stated or not, the FDA recognizes that they don't have all the answers and that this new aspect of diabetes drug development will be a learning experience for them as well as the industry and the diabetes research community more generally.

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#### GETTING ENOUGH PATIENTS

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**KELLY:** As a side note how many addressable patients are there that have quite advanced diabetes who are able to go into studies?

**DR. ORLOFF:** This gets complicated, but it's fair to say that the patients who are sick, who have active diseases of various kinds that are complicating their management as well as their lives, are less likely to be willing to participate in a study. Furthermore, there is an added level of complexity because of the fact that many of them will be on multiple anti-diabetic agents from which they cannot always be withdrawn for purposes of “clean” study design (i.e., either studies of the new drug as monotherapy or as add-on to specific agents). If glucose-lowering studies are to be conducted in such patients, the basic designs and objectives of these studies will by definition be different from the studies that have been standard for labeling of anti-diabetic agents.

**KELLY:** Is it ethically appropriate to try to enroll sick patients?

**DR. ORLOFF:** The short answer is yes, as long as the study is appropriately rationalized and designed. As I touched on earlier, perhaps without sufficient elaboration, I think that prospectively, one will have to plan a phase 2 or 3 development program that is going to differ from the standard of studying populations in which the CV event rate is well below 1% and instead enroll one where the CV event rate might have to be on the order of 2% to 3% (which may be the highest achievable rate). To propose to do that raises a lot of issues about being able to accomplish the historical objectives of the traditional glucose-lowering studies, which include demonstration of glucose-lowering efficacy and characterization of general safety and tolerability.

The other thing we need to understand is if you're done with phase 3, you go back, pool your events, and see how they play out, and take it from there. However, if you're starting out in a program, you are talking about what the plan going forward for the drug is. In such cases I think it's worth considering proposing a different kind of development program in which the study of glucose-lowering efficacy and general safety is done based upon a much more limited set of clinical trials and overall database with the idea that you don't need 5,000 patients in phase 2 or 3 to understand whether a drug lowers glucose. What you need are appropriately conducted and monitored studies. You need to look very carefully at what your pre-clinical signals are for organ-specific toxicity, but you can prove

the concept and enable the labeling of the drug with regard to its expected effects on glycemic control based upon much more limited set of trials. The reason for the very large phase 2 or 3 patient pool from glucose-lowering studies in recent years has been not in order to prove that the drug lowers glucose but in order to provide the requisite number of patient years or patients exposed to show that the drug is safe and well tolerated.

After a more limited glucose-lowering study set, the other important piece of phase 3 becomes a safety study that is not a glucose-lowering hypothesis testing study necessarily. For example, patients who are at high risk because they have diabetes and have already had a recent cardiovascular or cerebrovascular event would be randomized to test drug or comparator(s), but in this instance, the protocol would not dictate the management of their diabetes (i.e., by restricting treatment to the study treatments either alone or added to ongoing therapy). Rather, patients might simply be followed up and managed according to usual care standards with the only constant in their regimens being the study treatments to which they were originally randomized. Indeed, in such a study, all patients would likely come to the same place on study with regard to glucose control, so the study would not be a test of the benefits or risks associated with different levels of glycemic control. It would be a study of the safety and tolerability of a *treatment regimen* which included the new drug versus the comparator(s).

**MELISSA:** What about therapies intended for use early in the disease course? Studying these drugs in an “advanced diabetes” population may not be representative or informative for the intended real world use. Is testing these drugs in advanced disease ethical for the subject? Is it good clinical research in your opinion?

**DR. ORLOFF:** I’ve no doubt that the FDA accepts that early intervention to control glucose as well as CV risk factors in patients with type 2 diabetes is critical to improving long term outcomes. Studying safety and efficacy of new drugs in patients with longstanding disease and greater “accumulated” CV risk because of extended exposure to risk factors and atherosclerotic disease mediators arguably presents the “worst-case scenario” safety and tolerability profile of a drug. As such, when feasible, it certainly makes sense to include patients at high risk for CVD in clinical trials of new diabetes drugs, though as I’ve said previously, I question whether the usual glucose lowering and general safety studies are best served by inclusion of such patients, and whether such patients are necessarily appropriate for these trials. Finally, in the event that disease modification early in the course of type 2 diabetes is a critical objective of a study or drug development program, then the nature of the development program and in particular the means to address the CV risk exclusion standard that FDA has established will need to be discussed with them.

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## NUMBERS AND TIMING

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**KELLY:** Is there a concern that some companies won’t have enough patients or studies to examine for the meta-analysis?

**DR. ORLOFF:** There is absolutely. In many instances, there will be too few events in an ongoing or completed program to anticipate meeting or actually meet the FDA risk exclusion standard. I don’t know what the FDA will do for programs that have enrolled their phase 3 trials. The numbers of events that are likely to occur over the courses of the studies are set at that point. It is unclear whether the FDA is going to say to those people, “Sorry, you’re going to have to go back and get us some more events before we can evaluate this drug fully.” This would be the implication of their letter and guidance. Remember, this is about being able to define the limits of confidence in the CV safety of the drug. No more hand waving or statements about “appearing” safe. They want a number.

**MELISSA:** If you finished phase 2 and/or phase 3 and you can’t do a meta-analysis (that is, there aren’t sufficient total events in the pool of studies), then you do have to plan a trial where you would be able to show this number of events over a reasonable length of time. Is that right?

**DR. ORLOFF:** Yes. We are talking about a bunch of trials of sufficient size and duration, nothing less than six months or a year, in order to get the number of events that you need.

**KELLY:** It seems like the company may benefit because they can prove the glucose-lowering more easily, but they still have the major hurdle of enrolling enough patients for a cardiovascular outcomes trial.

**DR. ORLOFF:** It's certainly a new barrier. However, there is a potential silver lining because this extra upfront investment will by definition provide a higher level of assuredness about the risk-benefit profile for the drug.

**KELLY:** Historically, companies have not incorporated multi-thousand person, multi-year trials into capital planning. How will companies afford to innovate in your view?

**DR. ORLOFF:** It's undeniable that some programs will be dropped, whether developing additional members of established drug classes or fully innovative treatments. We must hope that the cream still will rise to the top and that truly valuable therapies will continue to be developed. I want to emphasize that these may be members of approved classes. Remember that if statin drug development had ended with Mevacor, we would not have the rest of the class, including Lipitor and Crestor, that have been shown to be extremely safe at doses significantly more effective than the originally approved doses of lovastatin. We need to acknowledge that there are justifiable reasons for this FDA stance. We can throw in the towel, or we can go to work and find out how to actually get this done and then explain to investors that the value proposition still remains.

As I see it, though, this has come at a particularly inopportune time. There is little money just sitting around and investors (whether the companies themselves or venture types) are tightening up their belts. In general, the FDA has raised the degree of difficulty and the price tag of diabetes drug development. So, we're just going to have to weather this. In the end, if there is a good drug that's coming through pipeline, it will benefit patients and will succeed. I have to have faith in market principles.

**KELLY:** Is it likely that these trials could take as little as a couple of years? That seems hard to estimate given that it is event driven. If it is event driven, you have the incentive to enroll patients who are sicker, but then are the results generalizable?

**DR. ORLOFF:** I really don't know for sure, but I would venture that size constraints will mean that the studies may take closer to three or more years. The more patients and the higher the population risk, the faster you get your answer, but a very short study may be criticized as not being a fair assessment of "long-term" safety. As far as generalizability goes, arguably the worst-case scenario for the drug's safety profile will be modeled by the study in sick patients. Extrapolating from that study to more stable, less medically complicated patients, one could reasonably speculate that the drug could only be safer and better tolerated. If the background "noise" of adverse events is too great in the "sick" population, you may actually miss certain safety and tolerability signals. So I think you need studies across the spectrum of disease severity and concomitant illness to best characterize drug safety. That is why we do a series of special populations studies in most programs.

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## **WORRIES ABOUT INNOVATION**

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**KELLY:** What are the implications from the FDA letter on drug development and innovation? From a patient perspective, just so you know my bias, I'm very worried about innovation being slowed.

**DR. ORLOFF:** I think it is quite clear why various constituencies interested in the development of drugs for diabetes would find this very troubling. For obvious reasons, it would seem undeniable that this is going to increase the time and direct dollar costs of developing diabetes drugs. I suppose it will also tend to add additional risk to drug development in this therapeutic area. One would imagine that there are those who are seriously considering whether it's time to move into other areas of new drug development as a consequence of this perceived raising of the bar for diabetes approvals. However, I suggest that it is very important to understand the reasons the FDA has moved to this standard, and why there may be a silver lining in what many perceive as a dark cloud.

With this letter and the guidance that followed, at least for diabetes therapeutics, FDA has responded to a crisis in confidence in the pharmaceutical industry, and in the FDA itself. The crisis amounts to the fundamental question whether FDA and industry, through current processes and procedures, can bring forward new drugs which will deliver on the promise of “safe and effective.” This is a broad-reaching crisis in confidence that involves FDA’s multiple constituencies, including the general public, the healthcare community, the Congress, and clearly much of the press, both lay and medical/scientific. Regardless of the merits of the criticisms, the situation is what it is and a concerted effort is needed to rebuild confidence in the “system.” FDA is attempting to achieve overall greater transparency of approach and to better “define” the limits of assurance of safety.

Overall, there appears to be a broad consensus that there is a need to know “more” about drug safety at the time of approval. This has, at least initially, been a particular concern for drugs that fall into the category of long-term therapies for chronic non-life threatening illnesses, of which diabetes is considered one. We all know that non-life threatening is a confusing label to apply to diabetes but when the regulatory world deems the disease non-life threatening, it means not *immediately* life threatening.

First of all, I don’t believe that raising of the evidence standard for approval is a sign or signal of FDA’s loss of commitment to bringing new therapies for diabetes to market. I think that if you sit down with the diabetes team at the FDA, you will understand that they do believe the public needs safe and effective drugs for the treatment of type 2 diabetes. I won’t put words in their mouths, but I imagine they would take the position that this guidance is a formal statement of commitment to all of their constituencies to best ensure a pharmaceutical armamentarium with a favorable risk-benefit balance established from the point of initial marketing. In other words, getting drugs to market with more assuredness, less doubt, and fewer questions as to what the true balance of risk and benefit is. I think the FDA recognizes it is necessary to restore confidence in the system. So, I think the intent is that we and everybody else will know more about risk versus benefit associated with the chronic use of these drugs. We will be closer to the truth with regard to understanding risk versus benefit than we are now.

**KELLY:** It seems like the FDA really wants to avoid all risk, which is very understandable. But is this possible? Doesn’t zero risk really mean zero innovation? And to what extent does the FDA worry about the current environment – it seems fairly clear there are systemic problems and that new alternatives would be very welcome. Making sure they are safe is very important, and I doubt anyone would advocate fewer safety rules – but the current ruling is hard to characterize as reasonable. Are there examples you can cite that help lend insight?

**DR. ORLOFF:** Many people have framed the whole discussion as an issue of over-reliance on biomarkers for inference of benefit of drugs. FDA accepts that lowering glucose in patients with diabetes is a good thing. Indeed, they do not require formal proof of clinical benefit of diabetes drugs. Lowering HbA1c is sufficient. However, they and some of their advisors do not feel that cardiovascular safety can be adequately assessed without formal demonstration of the absence of adverse effects, as measured by clinical cardiovascular outcomes (that is, things like MI, stroke, and sudden CV death). I would venture that the intent is laudable, but it is unfortunate that they have applied a one-size-fits-all safety “work up” for diabetes drugs, without regard to mechanism of action, anticipated side effects based on animal studies, as well as the clinical and laboratory side effect information that emerges from the clinical studies themselves. The FDA’s 2007 diabetes guidance actually made the point that the need for formal CV safety studies would be based on “signals” of CV risk, but the implication was that each drug would be considered individually as to whether extensive CV outcome information was necessary. In the end, they have chosen to require formal exclusion of CV risk of an “unacceptable” degree for all drugs for type 2 diabetes, save insulin, to this point.

**MELISSA:** Could we get your view about the FDA and its responsibility to patients?

**DR. ORLOFF:** The FDA is charged with the regulation of interstate commerce in drugs. The drug regulations are ultimately based on the concept of full disclosure — truth in labeling drugs. The key point is that everybody involved in using them understands the risks and the benefits. By definition, the FDA has a commitment to

individual and public health. That commitment is not just to ensure that drugs are safe and effective, but it also is to provide support and direction to the regulated industry in order to bring good products to the fore for patients in a timely and efficient manner. In other words, it is not there to stifle innovation or development. It is supposed to be a guide and ultimately a facilitator to getting products that are safe, effective, and of high quality from a manufacturing standpoint, to market.

When and if there is manifest evidence of a drying up of new therapeutics development and licensing of drugs for diabetes, then people will have to take another look at the regulatory standard for approval. As you know, the way the world works is that until you have the evidence of the adverse effect of the government's action or inaction, you're not going to have a good case to make to change the system.

**KELLY:** Our main concern is that it will slow innovation down.

**DR. ORLOFF:** One would hope that there will be a middle ground. The FDA letter is brief and concise; it offers the opportunity for discussion and sets a standard of evidence. It doesn't say how you're supposed to get to that point, but it gives some suggestion. One additionally wonders whether FDA will exercise discretion, say in the instance of a drug that didn't necessarily have the full number of requisite events to meet this statistical standard, but for which there was absolutely no signal and where there was a trial ongoing. That is, would they negotiate a post-approval commitment to finish the study and make continued marketing contingent upon the results of that ongoing study? As you know better than I, the sooner the anticipated revenue stream for the drug, the more likely it is to get funding. I should say that everything begins with the premise that the armamentarium is far from replete and that we still have a huge global public health problem in type 2 diabetes.

**KELLY:** The treatment costs of diabetes from 2002 to 2007 rose from \$24 to \$27 billion according to a January study in *Diabetes Care*; meanwhile the published costs of in-hospital care for people with diabetes, which we assume is driven by complications, increased from \$25 billion to \$58 billion. It seems more should be done to prevent patients for moving from the "well" patient to the "unwell" patient group.

**DR. ORLOFF:** I agree that it is wrong to think that we've solved the problem. People need to address or raise the question of whether there may be some sort of a negotiable middle ground here.

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## FAVORING CARDIO-PROTECTION

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**KELLY:** The new rules would seem to dramatically favor drugs that could be cardio-protective – and certainly a cardioprotective drug would be quite an addition to the diabetes therapy armamentarium. To close, could you comment on this potentially optimistic note?

**DR. ORLOFF:** Patients lose weight on GLP-1 and their blood pressures come down on GLP-1 and their lipid profiles improve, along with their diabetes. So either the primary action of the drug or secondarily the metabolic effects of GLP-1 are apparently overall very favorable. So, perhaps you are asking whether the new standards should take into account the effects of a new drug on indicators of CV risk and tailor the precise requirements, specifically regarding timing of the CV safety "exercise" relative to approval, depending upon the characteristics of each drug. In short, I think the FDA is going to be hard-pressed to do too much of this. It becomes extremely difficult to avoid a real or apparent "un-level" playing field. It would be nice if the FDA were willing to consider approval of certain diabetes agents under the contingent approval provisions of the new drug application regulations, so-called "subpart H." Applicable to new drugs for serious or life-threatening illnesses (which might require re-classifying diabetes on this score), this section provides FDA with the tools to approve a new drug on the basis of adequate well controlled clinical trials "establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely based on epidemiologic, therapeutic, pathophysiologic or other evidence to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirements that the applicant study the drug further to verify and describe its clinical benefit where there is

uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate outcomes.” So, in short, drug gets approved because of presumptive benefit based on an endpoint short of morbid and mortal outcomes, but with the formal proof of benefit to come from a study completed post-approval. And, of course, if the drug fails to show that requisite clinical benefit (or shows harm), then the approval is revoked.

After all this, let me add, though, that it has been and will continue to be extremely difficult to prove, experimentally, CV benefit associated with a specific diabetes drug. The question of CV benefits associated with glucose lowering per se is highly complex and studies comparing different intensities of glycemic control for their effects on CV outcomes are not likely to continue to be done. In addition, in studies comparing treatment strategies to achieve similar degrees of glycemic control in type 2 diabetes, whatever glucose-independent apparently beneficial effects the test drug might have on CV risk factors (i.e., blood pressure, lipids) will be readily balanced by available risk-factor modifying treatments prescribed to patients in the comparator groups, thus negating, potentially, the contribution of those effects to any difference in outcomes between the group treated with the test drug compared to the control.

**MELISSA:** This is a lot for us to think about Dr. Orloff! Thank you so much for making time to speak to us.

**KELLY:** I echo the thoughts – much, much appreciation to you.

-- Kelly L. Close and Melissa Tjota, Close Concerns

*Close Concerns publishes Closer Look, a real-time a real-time news service covering business goings-on in diabetes and obesity. Kelly is also editor-in-chief of diaTribe, a free online newsletter focused on new research and products for people with diabetes (diaTribe.us). Kelly and Melissa and their colleagues at Close Concerns attend over 30 conferences globally focused on diabetes and obesity, cover key medical literature in the field, and write regularly about over 50 private and public companies in the area. Kelly’s passion for the field comes from her extensive professional work as well as her personal experience as a patient with type 1 diabetes for over 20 years. This interview was originally published in slightly different form in the January 23, 2009 edition of Closer Look and in the February, 2009 Diabetes Close Up, a monthly newsletter they publish on goings on in the field.*