INTRODUCTION

The attached is the introduction to our 400-plus-page report synthesizing diabetes goings-on over the last 18 months. For ordering information, please see www.closeconcerns.com.

We spend all day, every day immersed in the business of diabetes, and in so many years of collective patient and market experience, we can say that there has never been a time in diabetes like today. Throughout the 1980s and 1990s, apart from insulin analogs and TZDs, innovation in this field stagnated, producing little more than a few generic drugs. In recent years, however, the explosion in diagnoses of type 2 diabetes, pre-diabetes, and related metabolic disease has sparked a flurry of innovation in pharmaceuticals and devices. In 2005, we saw the first new drug approved for type 1 diabetes in more 90 year**s**. We watched as Byetta was approved *sans* panel meeting. In the early days of 2006, we pored over 24,000 words devoted to diabetes on the front page of the nation's leading newspaper.

Yes, much has happened in this past 18 months. This volume, *Diabetes Round Up 2*, is intended as a comprehensive guide to the exciting events of 2005 and 2006 – what they mean for patients, companies, payers, and investors.

Below are our key learnings from 2005 and early 2006. In this report, we discuss what they mean for the diabetes market this year and beyond.

NOTABLE TRENDS IN 2005 AND 2006

Diabetes declared a mainstream presence.

As diabetes continues to grow, swallowing almost everything in its path, more and more Americans—as well as Europeans and Asians and Africans—suffer from diabetes or know someone who does. New 2005 statistics from Atlanta's Centers for Disease Control announced that 20.8 million Americans now have diabetes, up 14% since 2003. Up 14%! Diabetes is growing faster, from a *higher* base! Diabetes now affects an astonishing 7% of the U.S. population (10% of adults over 20, and 20% of adults over 60). Diagnosed patients are now estimated at 14.6 million, with an additional 6.2 million undiagnosed—the "missing millions." In minority populations, the increases were particularly daunting. Since 2003, there was a 20% increase in diabetes in non-Hispanic blacks, up to 3.2 million, and a 25% increase in Hispanic/Latino Americans, to 2.5 million and a 9.5% prevalence. One of three children born in the year 2000, goes the now-oft-cited statistic, will be diagnosed with diabetes sometime in their lifetime. This is even higher even more often for minority children, such as Hispanic females, who have a 50% chance of getting diabetes.

The rapid rise in the number of those with diabetes has not gone unnoticed. In January, 24,000 words were devoted to diabetes on the front page of the nation's leading newspaper.[1] The *New York Times* series highlighted the ravages of type 2 in New York City. Three top reporters spent a year focused solely on diabetes. Each piece of the four-part series zoomed to the top of the *Times'* "most emailed" stories list. Again in New York, the city mandated reporting of A1c results. These results are being tracked to assess the control of patients in NYC—and the success of providers.

[1] See our DCU #56 for our take on "Bad Blood," the *New York Times* series, and our interviews with the authors.

While controversial, it may be a way to gain a foothold on the massive public health problem that can't seem to be stemmed.

Diabetes invaded the public's consciousness last year in other, more insidious ways as well, staking its claim on the next 50 years of American health. Statistics released in 2005 in the inaugural issue of the *Journal of Pediatric Obesity* (first of all, how crazy that there is a need for such a journal?) report that more than half of children in North and South America will be overweight in fewer than four years, by 2010. Experts are predicting an epidemic of early heart attacks, strokes, and yes, type 2 diabetes, that will make this generation the first to have a shorter life expectancy than their parents.

Diabetes made its presence known in popular culture in more positive ways in 2005 as well. The first season of dLife, a TV talk-show style program intended for viewers with diabetes, premiered on CNBC. It featured former Miss America Nicole Johnson Baker as the main anchor host and invited guests like Dr. Aaron Vinik, Dr. Francine Kaufman, Dr. Lois Jovanovic, Dr. Steven Edelman, and other luminaries. Direct-to-consumer advertising of diabetes products is going strong, and Dr. Steve Edelman's Taking Control of Your Diabetes organization has more than taken off. When diabetes can support its own TV show, it appears it has entered the mainstream. (See our website to download the episode, "Empowerment" that featured our own Kelly Close discussing the latest drugs and devices, including incretins and continuous monitoring.)

As diabetes continued to grow at an exponential rate, options for diabetes treatment expanded.

Amylin's Byetta was approved by the FDA with no panel[2] – imagine, a drug for diabetes with a side effect of weight *loss*? It is a brave new world! In January 2006, inhaled insulin was also approved, albeit to the chagrin of two pulmonologists on the FDA panel who voted against it. Near-term, at pricing of ~$5/day, we doubt many payors will cover this, at all – especially since they've seen that patients really aren't that afraid of shots after all! (See: Byetta) Elsewhere in injectables last year, Novo Nordisk completed its insulin analog portfolio with the addition of long-acting Levemir. Sanofi-Aventis countered with a short-acting insulin, Apidra, to complement its blockbuster long-acting insulin, Lantus.

Ironically, the company that first commercialized insulin and was long synonymous with the product, Eli Lilly, is the only one of the three without a long-acting insulin analog—a critical insulin for growth going forward, in our view. Symlin was approved as the first new drug for type 1 diabetes since the discovery of insulin. This drug affects post-prandial blood glucose scores in spades, and patients on it keep talking about it as a happy drug—again, a drug that prompts weight *loss* is unheard of. The buzz over rimonabant—Sanofi Aventis's potential solution for everything from gambling to smoking to obesity to diabetes—culminated only in an approvable letter for weight management in early 2006. This suggests that obesity drugs require a lot more work before they go mainstream, even though the drug got European approval later in 2006 and we look for U.S. approval to emerge eventually, even if in the midst of CNS misgivings. DPP-4 inhibitors, including Merck's sitagliptin and Novartis' vildagliptin, have now been submitted to the FDA and BMS' saxagliptin should follow soon enough; we provide a breakdown of the new incretin classes later in this report in our new product review.

[2] For the uninitiated, most new drugs need approval by a panel of experts pulled together by the FDA. It was a major surprise that the FDA deemed that no panel was needed for exenatide (Byetta); indeed, the relative safety of this drug has emerged as one of the drug's biggest benefits in this time of the Vioxx disaster.

There is still no magic bullet.

Despite the expansion of the armamentarium, there is no magic bullet for diabetes. This is what makes endocrinology and diabetology especially challenging as compared with other specialties that have, say, therapies like statins—a clear drug choice with irrefutable evidence and dramatic effects in patients; no wonder that class has close to a $30 billion annual global market (and, albeit, falling, with the new entry of generics this year). If anything, in the last couple of years, treatment paths for type 2 diabetes became decidedly more diffuse. The treatment for diabetes is anything but straightforward or one size fits all. As each new option comes onto the market, healthcare providers must decide how that changes their treatment plan for type 2 diabetes.

In this volume, we explore the new treatments and assess how these are changing treatment paradigms. To what extent will Byetta delay the move to insulin? Will more patients actually back off insulin (unlabeled at this stage though it is)? Will a type 2 try a DPP-4 inhibitor before Byetta? With metformin? Instead of metformin? Which patients will be good candidates for inhaled insulin? Yes, metformin remains the first-in-line therapy for type 2 diabetes and we look for this to persist. However, we look for sulfonylureas, with their associated hypoglycemia and weight gain, to soon be eclipsed by the new options – and not a moment too early, in our view.

Cardiology became a larger part of diabetes.

A minor, but telling, data point: at a 2006 conference on advanced glycation endproducts sponsored by the ADA, we heard a world-renowned cardiologist plaintively proclaim that "diabetes is a vascular disease that sometimes manifests itself as hyperglycemia." At the Canadian Diabetes Association, a well-known endocrinologist posited that "cardiologists will soon be prescribing insulin." We've heard over and over again that upwards of 70% of people with diabetes die from heart attack and stroke. While the morbidities of diabetes—blindness, neuropathy, kidney failure, and the like—perhaps are most feared, cardiovascular disease is the most common cause of mortality. As such, doctors are mounting a fight against CVD, advocating for aggressive control of lipid and cholesterol levels. In some ways, it had begun to spark a turf war between cardiologists and endocrinologists, who say that cardiologists are attempting to poach their patients. In more recent days, AHA (American Heart Association) and ADA (American Diabetes Association) are trying to patch up their differences in various areas such as metabolic disease. In our view, the semantics on this one should just be left aside and the disease, such as it is (and we believe it is) should just be treated.

Yes, the precise connection between hyperglycemia and macrovascular disease has historically been controversial. Last year's release of the Epidemiology of Diabetes Interventions and Complications (EDIC) results—the follow-up study to the Diabetes Control and Complications (DCCT) trial—proved indisputably that patients in the intensive control group had significantly lower mortality and a lower risk of cardiovascular events. This study, which began in 1994, found that intensive treatment lowered the risk of heart attack, stroke, or death by 57%. Check that out – pretty hard to ignore. We're waiting for results in a major type 2 trial to corroborate this type 1 evidence.

We've seen the merging of cardiology and endocrinology in other ways as well. The results from the FIELD trial—Fenofibrate Intervention and Event Lowering in Diabetes—were announced last year at the American Heart Association meeting. The focal point of last year's annual meeting of the European Association for the Study of Diabetes (EASD) was the release of the results of PROactive, a study that examined whether the use of pioglitazone, a TZD, would lower CVD risk. FIELD was a negative study, saying nothing conclusive about fibrate use in diabetes, and PROactive failed to meet its primary endpoint, though it did show a 16% reduction in risk of heart attacks, strokes, and premature death. We believe that had these study results been more

strongly positive, the focus on cardiovascular health in diabetes treatment might be even greater now.

Perhaps the most intriguing interaction between the two fields of late took place on the pages of the *New England Journal of Medicine*. After an FDA panel recommended BMS's muraglitazar, for approval, cardiologists at the Cleveland Clinic led by Dr. Nissen analyzed the publicly available data to argue that the drug posed a serious cardiovascular threat. Muraglitazar (also known as Pargluva), a first-in-class dual-PPAR designed to tackle triglycerides, cholesterol, and blood sugar all at once, received an approvable letter, a surprise—and relief—to many, after the panel's decision to approve and a clear testament to the influence of the editorial pages of *NEJM*. Earlier this year, it was *deja vu* as Sanofi expressed incredible confidence over rimonabant, but the CNS side effect profile – and massive trial drop-outs - appeared worrisome to some. Indeed, perhaps the biggest learning was not to stop worrying when nothing was said about a panel meeting! Some investors had begun to celebrate when they heard there was no panel, but when *JAMA* published the editorial, that was nailing the coffin shut, in our view, and delay ensued. Indeed, the power of the clinical press impressed us more than once in terms of editorials and we'll continue to be watching these and ensuing impact.

Reimbursement loomed large in diabetes' future.

January's approval of Pfizer's Exubera, the first-in-class inhaled insulin, marked yet another new option for patients and a potential market blockbuster, but reimbursement remains an open question—on which the success of the therapy hinges. This is true not just for inhaled insulin, but also for continuous glucose monitoring, obesity therapy, and many other new or imminent drugs and devices. Companies are growing increasingly savvy about conducting clinical trials and designing a publications strategy for their products, as evidence-based medicine has become paramount for both medical professionals and coverage. Companies now know they need to conduct and publish trial results in peer-reviewed journals before their drug or device will be taken seriously. The power of managed care also continues to grow, and that's usually bad news for patients. It means higher co-pays, fewer payment approvals, more requirements for doctor approvals, etc. Counterbalancing this may be the strength of the patient lobby. We've just begun to see this, and we look for it to be very important in 2007 and beyond.

Diabetes continued to lose valuable healthcare providers.

Reimbursement is squeezing our healthcare providers. Even as the ranks of those with diabetes swell, endocrinologists, diabetes specialists and the valuable CDEs are leaving the field, and fewer of the best and the brightest medical school graduates are specializing in this area. A main reason, of course, is that reimbursement for diabetes is weak, as it is for all specialties that lack procedures but require analysis, intensive management, and counseling. Medical school graduates with enormous debts feel pressure to enter a higher-paying specialty, and many endocrinologists are forced to try to see more and more patients and work longer hours to make ends meet. There are only 4,000 endocrinologists in the U.S.—fewer than that in full-time clinical practice—and there are now upwards of 15 million diagnosed patients.

We also have too few diabetes educators. At the AACE-sponsored Consensus Conference on In-patient Diabetes and Glycemic Control earlier in 2006, thought-leading CDE Geralyn Spollett of the Yale Diabetes Center noted that there are only 13,000 CDEs in the country now practicing, and the number keeps declining. It is well-known that our health care system, designed for acute care, poorly serves the increasingly chronic needs of the American people. Diabetes may need to be the pioneer in changing the model, because the epidemic is placing such a heavy burden on the nation's healthcare system.

The regulatory environment toughened.

The resignation in 2005 of Dr. David Orloff as the director of the FDA's division of drugs to treat metabolic and endocrine disorders, raised questions about how diabetes drugs would be received and reviewed at the agency. Dr. Orloff was known for his expertise in diabetes. Although replacement Dr. Mary Parks is very well-regarded, her expertise is outside diabetes. One wonders how drug reviews will move forward. While we have all the respect in the world for Dr. Parks, we can't help but wonder who at the FDA really grasps the nuances of diabetes. The FDA has seemed more eager to work with industry on diabetes-related products as of late, but there is still an enhanced emphasis on safety that is beyond appropriate. We'll have to watch how these two principles, or values, play out this year and beyond. How the two will intersect should make for an interesting year—and rest of the decade.

Continuous monitoring pushed the envelope, and we took one step away from A1c-centricity.

We are on the brink of an all-out revolution in type 1 thinking, and continuous glucose monitoring (CGM) will precipitate this shift. In 2005, Medtronic released its Guardian RT and months ahead of time, in 2006, got its 522/722 sensor-augmented pump approved. Competitor DexCom won approval for its STS continuous monitor earlier in 2006, and we expect Abbott's continuous monitoring technology to see approval in later 2006. We're about to watch the reimbursement battle begin in earnest. Will continuous monitoring become a thriving commercial market? Yes, but more slowly than perhaps seems right.

Now that we have good technologies that have moved far beyond GlucoWatch and CGMS—which were very important stepping stones in their own right, but not technologies ultimately ready for prime time—we believe that patient demand is there. However, bottom line, *when* continuous will become a real market, where the technology is not only available but also accessible, depends almost entirely on reimbursement. We saw a lot of controversy last year over labeling, over replacement-this, and replacement-that and we certainly hope that reimbursement won't ultimately depend on the right labeling, or we'll be waiting light-years. We think about it a different, simpler way—reimbursement should depend on *evidence showing better care*. For us, reimbursement should be a no-brainer because we are so certain this technology enables better outcomes, even with the first-generation "real-time" products, limitations and all. We salute JDRF, an organization that has stepped up to help industry make sure a market develops and that innovation continues strong. We expect that by 2008, we will be much more sure on the reimbursement front. Much before that? We hope so, but we don't expect so.

That said, we feel continuous glucose monitoring will revolutionize diabetes. With conventional episodic monitoring, a typical patient who is "intensively managed" knows his or her exact blood glucose approximately four times during every 24-hour period. Even the hyper-intensively managed patient perhaps knows 10. With a continuous data stream patients will have access to blood glucose data for every minute of every day and with the best products and will know the direction that the blood glucose is moving. That is breakthrough! For the very first time patients will be able to act *proactively* to avoid hypoglycemia and hyperglycemia rather than only *reactively* once these have occurred.

Importantly, healthcare providers and patients paid closer attention to glycemic variability.

Thought leaders are questioning, more than ever, whether this may contribute to both short- and long-term complications. Continuous monitoring will uncover once-invisible postprandial spikes, nocturnal hypoglycemia, and the glycemic instability that type 1 patients, in particular, experience, and it will provide the technology to evaluate in a formal study the effects of

glycemic variability on both short- and long-term health. Likewise, increased attention to glycemic variability will generate additional incentive for providers and patients to explore CGM. The A1c test has for so long been the standard of whether or not a diabetes patient is in good control—and it is widely acknowledged to be imperfect—but it was the only tool we had to approximate 24-hour glycemic control. With CGM, that is no longer true. But CGM extends beyond a tracking tool; we only saw the tip of the iceberg of what CGM will do as a therapy. The Medtronic Guard Control trial results announced at EASD in 2005 may have been the first diabetes trial ever to show a simultaneous reduction in both hyperglycemia *and* hypoglycemia, and this was in patients who used the continuous monitor with no specific instruction. When one really thinks about how patients have been managing, with how little data, the future is exciting, indeed. Data from DexCom and Abbott at AACE and ADA in 2006 corroborated Medtronic's early successes, and all in all, we think the technology is headed for success—but success over time.

The investment community missed the mark a bit.

Not on all counts. But take, for instance, Wall Street's assessment of Symlin, a natural hormone made by Amylin Pharmaceuticals that is normally co-secreted with insulin – just not in patients with diabetes. Let's follow its logic. Type 1 is a small market—check.[3] Symlin is complicated to use—check. This drug will not be a money-maker—not so fast. First, we expect Symlin sales to build as the treatment of type 1 begins to focus on glycemic variability and not only on A1c. Patients will seek ways to smooth postprandial spikes, and this cannot be done with insulin alone. Second, we see continuous monitoring making it much easier to use Symlin. Third, there are serious untapped markets: for example, type 1s who want to become pregnant. This is called "pre-conception" mode, and many patients don't ever make it out of this mode because pregnancy requirements are so rough. This is a market waiting for Symlin. Call us nuts—we know pregnancy studies are never at the top of anyone's list—but the drug could make an enormous difference here. And the market isn't so small, with 135,000 type 2s and 12,000 type 1s pregnant every year. Thirdly—and this is where we expect you to perk up—we see vast market potential for Symlin in obesity. The trial results have been positive, and the dosing is considerably simpler because there is no related insulin adjustment *or* any fear of hypoglycemia. We elaborate more on our view of different products inside, but for now, we see Symlin as a potential sleeper obesity blockbuster.

Likewise, Wall Street has undervalued Amylin's other drug, Byetta, largely due to the injection issue. In our view, with average revenue estimates for 2006 at under $400 million, as we said all last year, we think the street hasn't yet even begun to comprehend the speed at which Amylin is moving. Perhaps most importantly, the potential for market expansion is virtually limitless as Amylin is moving both directions; we ultimately look for Byetta to treat advanced diabetes as well as pre-diabetes. Great news for patients, we say. Of course, neither Byetta nor Symlin is for every patient, but the numbers who could be helped are far, far above what early trialing shows.

M&A was very active.

J&J purchased Animas in December of 2005 for $518 million in cash, uniting the #1 glucose monitoring company with the #2 pump player. Only six months prior, in June of 2005, the #1 pump player Medtronic acquired Transneuronix, medical device company with a device therapy for obesity. In July 2006, Bayer announced that it would acquire Metrika. To the extent that these

[3] Although it has long been thought that the type 1 market is growing only at the pace of population growth, this is probably an old wives' tale. There's no registry, so we don't really know for sure, but it's our guess that that 1 million US population figure for type 1 patients that you've heard for so long – or 1.3 million is really aggressive circles – is actually a bit higher and is growing at a *particularly* fast pace in adults.

acquisitions allow companies to integrate technologies and move more efficiently, we hope that they will be in a better position to accelerate solutions for patients and advance progress on the artificial pancreas.

The ADA/EASD eliminated metabolic syndrome.

We'd like to report that they cured the world of metabolic syndrome, in a manner reminiscent of vaccines and polio, but rather what we mean is that they disputed the validity of the diagnostic category. Announced a few days prior to EASD 2005, the joint statement suggested that a syndrome must consist of something more than the sum of its parts and must have a clear etiology, and that metabolic syndrome did not measure up. We remain very intrigued by the question. This debate fits into a broader theme of changes in diagnoses. There is no longer only type 1 and type 2 diabetes, but also MODY (Maturity Onset Diabetes of Youth, a rare genetic form of type 2 that appears only in Caucasian teenagers) and LADA (Latent Autoimmune Diabetes in Adults, which appears in adults over the age of 25). We have "pre-diabetes," and, in a short time, we'll find out whether it can be treated with rosiglitazone or ramipril, when the results of the DREAM trial are released. With a market of over 40 million people in the U.S. alone, an effective treatment for pre-diabetes would be in high demand and might help to curb the alarming growth in type 2 diabetes. To the progression of type 2, we've added pre-diabetes, and we see the stage before that as obesity – a condition that is now being targeted pharmacologically. Diabetes and related metabolic disease have grown so fast that treatment has ceased to be a specialized branch of medicine. When nearly one in 10 have a condition, it becomes the province of the general practitioner, the public health system, and the population at large.

2005 was, in our view, a year for patients, and this is continuing strong in 2006. For the last decade, progress has been Lantus and some generics. Now, we have DPP-4s, GLP-1, TZDs, new pump technologies, continuous monitoring, Symlin, and hot new classes like PTP1B and HSD1. 2005 was a year of stunning drug launches and dramatic set-backs; a year in which we at Close Concerns jetted off to more than 30 different conferences nationally and worldwide (including New York, San Francisco, Atlanta, Prague, Belfast, Athens, Vancouver, Edmonton, DC, Chicago, Boston, Los Angeles, among others). In the next few months, we'll visit Copenhagen, Malmo, Cambridge, Toronto, Las Vegas, and Capetown—see our full report for conference guides for 2006, 2007, and 2008.

In this volume, we have amassed our collective knowledge through our copious notes from each of these conferences. We include detailed industry models for the $6 billion blood glucose monitoring market and the $1 billion insulin pump market. Our reports on half a dozen major 2005 and 2006 analyst meetings follow the models. Thereafter, we review the 50 top diabetes-related articles published in peer-reviewed medical journals over the past year, from *JAMA, NEJM, Diabetes Care*, *Diabetalogia, Lancet*, *Diabetes Educator*, and more. In the "Best of *Diabetes Close Up,*" you can find our top five stories from our monthly newsletter, *Diabetes Close Up*.

Our in-depth drug pipeline database consists of 30-plus companies developing hundreds of diabetes and obesity therapies. Thereafter, you can see the detailed calendar of over 100 important diabetes meetings in 2006, 2007 and 2008.

Looking at this calendar, we invite you to start learning as soon as possible, because more is happening every day. This is a dynamic time in diabetes, and we are excited to share our learning and our analysis with you. To order a copy of Diabetes Roundup II, please visit www.closeconcerns.com or send us a message at reports@closeconcerns.com. Onward!