

DIABETES CLOSE UP

Diabetes Close Up, V3, #14
October 26, 2004
Third Quarter Industry Update

The short version

Greetings! We've had a busier-than-usual summer and fall, but wanted to get some insights out to you before winter comes in earnest. See below, one dozen updates:

1. **Ten company reports for 3Q:** See more below on diabetes and obesity news from J&J, Abbott, Roche, Astra-Zeneca, Pfizer, Merck, Sanofi Aventis, Lilly, Novartis, and Aradigm.
2. **An extra-detailed report on Medtronic's analyst meeting** earlier this month, where management shared news on its strategy for continuous monitoring and pumps through 2009.
3. **Fundraising news** – Pelikan Technologies announced this morning it had closed a \$29 million series D fundraising round.

The longer version

Lots of major pharmaceutical and medical device companies have reported results for the third calendar quarter of the year over the last couple of weeks. With a few left to report, here's our review to date:

1. **J&J:** LifeScan posted sales of \$420 million - \$225 million in the US and \$195 million internationally. Excluding foreign currency gains, sales rose 5% in the US, and 23% overseas, for a nice gain of 13% worldwide overall. Sales had been \$400 million and \$420 million in the first two quarters of the year, respectively, so LifeScan appears easily headed for a \$1.6 - \$1.7 billion year in 2004, up from \$1.4 billion in 2003.
 - **International sales did very well:** Including foreign currency gains, sales rose 32% internationally, for a worldwide gain of 16%. This quarter, international sales totaled 46% of total LifeScan sales, the second highest percentage ever. Product diversion (a.k.a., the grey market) must still be a factor, though international sales do seem to be going strong and emphasis on international markets appears a major focus for LifeScan
 - **Easy comp in the US...**: Important to note, LifeScan faced easy comparisons in the US, where sales were flat in 3Q03, but J&J faced tough comps overseas, where sales had risen 32% in 3Q03 (including FX gains).
 - **And the US still appears a tough market** - would be interesting to see what is happening on pricing in the US, in particular, and to see if volume gains are much higher than 5%. Going forward, we will be looking more closely at pricing pressure facing the American diabetes industry, including the impact of Medicare competitive bidding in particular. Watch for an interview with reimbursement guru Bob Knorr in an upcoming issue.
 - **Focus on India:** On the product front, J&J noted that One Touch Horizon launched in India and will launch elsewhere in Q4 and 2005. Where else it will launch is a big question -- this looks like a great meter from a product feature perspective in that it's still 5 seconds, takes 1.5 µL of blood (not 0.3, but not bad, especially compared to Roche), and doesn't use Ultra strips, so shouldn't prompt any diversion issues. LifeScan showed this at EASD and got big attention despite a relatively small booth.
 - We saw the *Horizon* meter a few months ago when our crack reporter Melissa Ford flagged it out of nowhere in a major Indian newspaper. According to the article, the meter is priced at 1,500 Indian Rupees, about \$32, roughly one-third the price of existing monitors in India. <http://www.chennaionline.com/health/homearticles/2004/07/lifescan.asp>. The article notes that the Horizon had been developed over two years, with trials in India as well as Edinburgh and Birmingham, England.

- **How big is this market in India, anyway?** There is some skepticism that the market can be commercially successful, given the degree of poverty in India. Indeed, it is disquieting. Although average wages in places like China and India are difficult to determine since some areas are heavily industrial and others are heavily agrarian, we know that Indian textile workers, for example, earn \$0.20 - \$0.30/hour. Obviously with a \$32 meter, one can imagine that it's pretty difficult for patients with diabetes to fund their own self-monitoring needs.
 - Historically, the main testing method in such poor countries has been urine test strips – suboptimal because urine is delayed (one is always viewing a previous score, not a current score) and it is difficult, at best, to make insulin adjustments based on this. On the positive side, urine strips are very inexpensive for the government to provide. Visual blood testing has also been a popular method in such countries – logical, as there is no need for a device, and COGS are low.
 - That said, since India currently has the biggest diabetic population in the world – 35 million people¹ - one can imagine that the percentage of the population that can *self-pay* for medical care is actually not *that* small. Indeed, the reason to have meters in these markets is to capture the middle - upper class, which may not be large by percentage standards, but it's fair to say, is huge on an absolute number basis. This will be particularly true going forward: the percentage of the population over 50 in India should increase from 15% to 23% by 2025, according to IDF, resulting in an estimated 73 million patients with diabetes by 2025.
 - And that's just diabetes ... hold on to your hat. There are also an estimated 93 million patients with impaired glucose tolerance (IGT) in India currently, which is expected to grow to nearly 150 million by 2025.
 - **J&J report touches on obesity:** The company mentioned in its quarterly report that bariatric surgery is becoming a significant growth driver for the surgery business – this is the Obtech contribution – the product isn't yet on the market in the US. We'll be watching at NAASO for news on this front. Other obesity news wasn't extensive; there was no mention of testing Topamax (an epilepsy compound) to treat obesity and it is not listed on the official pipeline chart, though we do believe off-label usage contributed to strong Topamax results., even though it isn't being marketed as such. Topamax is now a billion-dollar product as of 3Q results (\$1,029 million in sales year to date), when US sales rose a robust 49%.
2. **Abbott:** Abbott Diabetes Care results for 3Q04 came in at \$210 million, up 45%. Management had earlier forecast sales to rise 40%. Most of the growth stems from the TheraSense acquisition – Freestyle Flash seems to be very popular among intensive testers, the most profitable demographic group.
- **On a reported basis**, US revenue for the combined MediSense/TheraSense business rose 108% and international sales rose 10%, including 6% benefit from currency.
 - **Product news:**
 - Freestyle Navigator is under active review and management noted that a key to success will be the ability to make a replacement claim on the label so that patients can make treatment decisions without fingerstick confirmation of blood glucose values.
 - Management noted that Abbott Diabetes Care recently initiated a 100-pt study, the results for which are expected in 2005. An FDA panel meeting should follow shortly thereafter, as would Navigator launch pending FDA approval.
 - The launches of Freestyle Mini (overseas name for Flash) and Precision Xtra continue to go well in Germany and Northern Europe.
3. **Roche**
- **Roche diabetes care sales grew 10%**, to about \$595 million (740 million CHF) for 3Q04. Although this still represents stronger-than-market growth, growth has slowed a bit - annual growth was reported as 15% in April and 12% in July. Management ascribed the moderately slower growth as “quarterly phasing.” We point out that pump sales are included in this figure – they are no longer broken out, and since only 9-month revenue is given, Roche also doesn't show incremental growth for the pump business. We estimate the pump business at about \$35-\$40 million for the third quarter and speculate

¹ IDF *Diabetes Atlas*, 2003, page 255.

- that growth slowed from a year earlier, since year-earlier numbers would've had some US revenue (the regulatory problems with pump happened in late summer, 2003).
- **US still slow...**: Roche does not break out geographic results, but management remarked that growth has not yet recovered in the US and it estimated that the US *market* (it didn't comment on exact Roche US growth) was growing 4-5%, "*5 ½ %, tops.*" It said European market was coming back, and growth prospects there were more positive. That said, it noted that the strong double-digit worldwide growth seen in past years was unlikely to return except in developing markets. We suspect the slower US growth has surprised people even internally; management had said at one point it thought growth might return in the US later in the year, but it was firm in noting this is not expected at this time. When questioned, management said the US business was growing "*at least as fast*" as the "*second biggest competitor in the market,*" i.e., J&J's LifeScan business.
 - **But Roche's run rate is very impressive.** Noting that worldwide growth in major markets used to be 12-14%, Roche now forecasts that even with a recovery, we'll see closer to 8-9% going forward. All that said, these are still stellar results – a run rate of ~\$2.4 billion is impressive, indeed.
 - **Channel divergence cited:** Management was surprisingly – and refreshingly – candid in characterizing reasons for the US slowdown, citing channel divergence as a major issue and noting that all competitors have underestimated mail order strength. Roche estimates that mail order is now at least 20% of the market (we believe it may actually be closer to 25%), up from 2-3% just a few years ago. Remarkable, in a word².
 - **Roche international presence strengthens in Asia with diabetes-related investments and inroads:** Similar to LifeScan, Roche has been at work in Asia.
 - With its partner Sanmina-SCI, Roche will produce Active meters in Shenzhen for the global market – management discussed how the new Shenzhen plant will help on both revenue (new market) and cost side (cheaper COGS). Eight hundred thousand meters, count 'em, are expected for the first year, which should optimize and complement facilities in Mannheim and Indianapolis, according to management.
 - In India, check it out, Roche now has a dedicated sales force. Again, while a low percentage of people have enough money there to pay for meters and strips the market is so flipping big that the absolute number of people that *can* self-pay is pretty large. There are at least 3 million type 1 diabetics and at least 20 million type 2 diabetics in China, and of course, type 2 disproportionately affects the affluent, who are more able to pay for testing and treatment. In India, as noted above, there are an estimated 35 million diabetics, but less than – perhaps *well* less than - twenty percent actively seek care at this time. In both cases, as these economies grow it is likely that diabetes will become more prevalent and increasing numbers of people in these countries will be able to afford better care. One can only hope.
 - Management gave some detailed stats on China in its slides, noting a 2.4% prevalence rate of diabetes (~21 million people), which is actually significantly lower in prevalence than the US, but obviously represents a greater absolute population size. It is estimated that 1.2 million Chinese patients are diagnosed each year, or 3,000/day - and one can bet this will increase as screening improves there. It is actually estimated that about one million patients are diagnosed in the US. This has increased dramatically in recent years with been diagnostics techniques.
 - **Two notes on the regulatory front for Roche:**
 - Management said it was preparing for an upcoming FDA inspection of its plant in Burgdorf at the end of 4Q. This is a delay from expectations they voiced in the first quarter, when they had suggested the FDA would visit the plant in 3Q.
 - Roche has recently submitted its 510-K for its new (and newly named) Spirit pump. Absolutely no details were available on Spirit. Roche wasn't showing this pump at EASD, to our disappointment, though it did show its first Accu-Chek branded pump (see product news below).

² One data point: Kelly's very own Blue Cross Blue Shield, for example, doesn't pay for her strips at drug stores any longer – it's their way or the highway, and they make her send away for them rather than allowing purchase at her favorite 24-hour Walgreen's in San Francisco's Castro district. Interestingly, they will still pay for lancets at Walgreen's, as well as for Novolog (up to 2 vials a month, although this is twice as much as a type 1 patient with her weight needs – would that insurance would pay for double the number of test strips that they desired!)

- **Details on the medical device product front:**
 - **Meters:** In February, 2005, the Accu-Chek Aviva will be launched. This will succeed the Accu-Chek Advantage platform. This is a big move, since Advantage has had great brand equity – it is in its 10th year and has annual revenues of 1.5 billion CHF, or about \$1.2 billion. That said, it has had very slow growth more recently, despite recent launch of Advantage III. Management wouldn't comment on product features except to mention "*new technology and unique safety features.*" Advantage growth year to date is 1%. It'll be very interesting to watch this re-launch.
 - **Attempting to further leverage the strength of Compact, Roche has a new Compact meter ready to roll out in 2005,** the Accu-Chek Compact Plus. For competitive reasons, Roche disclosed little about new product features, though we assume with Multi-Clix, it will continue to drive toward a more fully integrated product. Compact has been a very fast-growing meter and Roche has put a lot of marketing dollars behind it; year to date growth is 55%. Whereas Roche calls the Advantage its "*most dependable product*" it calls the Compact the "*most convenient product.*"
 - **Growth for other meter brands – Active/Go is up 9% year to date.** Growth was not mentioned for Complete, which appears to be de-emphasized.
 - **Pumps:** Management mentioned it showed its first Accu-Chek branded pump at EASD – the Accu-Chek D Tron Plus. It will have its European launch this quarter. This pump communicates with Accu-Chek blood glucose meters through Pocket Compass software – it is unclear to what extent this is automated. The newest pump has been named the Spirit – no details were given on this beyond description as "*next generation of highly dependable insulin pumps*" and characterization as the first pump to come out of Disetronic integration. Management said that pump sales in Europe were good and that consumable sales in the US were seeing "good" single-digit growth. It did not give an outlook for this business for 2005.
 - **Lancets:** Management spent a couple of minutes on lancet business, noting that this is a 400 million CHF (\$320 million) business and that Roche has 50% of the market, an estimate that we found to be surprisingly high. The SoftClix business is flat year to date. It discussed two new lancets:
 - The Accu-Chek Safe-T Pro Plus is for the professional market – it is a single-use device with three depth settings – global roll out should be complete in 4Q04.
 - The Accu-Chek MultiClix is for the consumer market. We saw this at AADE and at EASD – it is a six-lancet drum, built on the same idea as the Compact meter. As noted, we understand Roche is moving toward building an "all in one" integrated device, perhaps similar to what Pelikan has been working on. Management noted that the MultiClix lancing device "supports alternate site testing." We thought it looked like a good product when we saw it at AADE – it won't be out in the US until much later in 2005 from what we understand, but the global rollout began in Europe during Q3. Although there is a drum feature, it is still possible for patients to re-use lancets. It may sound boring, it's pretty high tech. Considering that many frequent testers do not regularly change their lancets now, it will be interesting to watch the consumer reaction.
 - **Software:** Roche is marketing Pocket Compass software heavily – appears to mention it whenever it can. This software uses commercially available PDAs and combines BG monitoring and insulin delivery information. Notably, it actually gives insulin recommendations as well. Roche is heavily marketing meter download/analysis software³.
 - **No discussion related to continuous monitoring.**
- **On the marketing front, Roche has lots going on.**
 - **Roche is increasing meter placements in the US** – it placed 5.2 million meters worldwide year to date, with 5.5 million in the plan. It is increasing with another 400,000 more meters,

³ **Press release excerpt:** Accu-Chek Pocket Compass 2.0, a software package for personal digital assistants, is another product expected to stimulate steady growth. It is the first commercial diabetes management software that allows users to download and combine data from both an insulin pump and a blood glucose meter. The new possibilities this opens up for analyzing data will benefit frequent testers in particular, enabling them to achieve even better glycemic control.

so will place 5.9 meters in 2004 altogether. We would estimate, at \$40-50 COGS, a total investment in the range of \$230 - \$300 million.

- **Commercials:** So we like Roche's Compact "Live Life, We'll Fit In" commercials, which we first saw on early morning BBC, a few months back. See our appendix for a full discussion – we like them so much we couldn't really summarize our enthusiasm in a paragraph, so for those really interested, please see our in depth discussion.
 - **Moving to pharma momentarily:**
 - **Nothing new was mentioned on Roche's R483**, the "novel TZD" in development. From the 2004 ADA abstract, it appeared that R483 may offer a better way to target PPAR- γ , as it looks to have higher affinity and binding. In light of the new guidance by the FDA on all PPAR drugs in development, Roche said it would wait for further long-term toxicity data to come in before making firm Phase 3 plans. Sounds like they are already in midst of rat studies and they will have data in 2005.
 - **Xenical results were not inspiring**, nor were Meridia results from Abbott. There is a serious unmet need here – we are finding Sanofi's Acomplia (rimonabant) potentially exciting, as are earlier-stage drugs in Amylin's pipeline. More to follow on this post NAASO (www.naaso.org).
4. **AstraZeneca: No real diabetes news**– AZ did recently acknowledge it would have a one-year delay on Galida, its PPAR agonist, which it now expects to file in 2007. They have this on their pipeline, incidentally, for type 2 diabetes as well as metabolic syndrome. While the potential market for metabolic syndrome is obviously very large (40 million Americans, for a start), the approval process could be inordinately difficult. Research is still underway, but it's presently unclear whether metabolic syndrome will be viewed by the FDA as a singular disease or a collection of related symptoms. With conclusive diagnosis of metabolic disease still less than crystal clear, it is difficult to say what sort of guidelines or performance the FDA will ultimately require to show prevention of diabetes (or for that matter, prevention of diabetes complications) – it sounds like three years at minimum. While we will follow this drug and this market carefully, it is anybody's guess as to when a metabolic syndrome or diabetes prevention indication could see the market. Certainly, however, this is becoming a much bigger area to watch and we're positioning ourselves front and center as there's much to learn in the next several years – to say nothing of now and of the coming months:
- **Journal watch!** On this front, there is an excellent article by Jay Skyler in the latest *Clinical Diabetes* that details, among other things, completed studies regarding impact of glucose management and the completed and ongoing studies regarding pre-diabetes, prevention, etc. The TZD studies discussed: DREAM and NAVIGATOR and ACT-NOW, where completion is expected in 2005, 2007, and 2007, respectively. This will be very key for prospects of TZD labeling for prevention of diabetes and we are all over watching this. <http://clinical.diabetesjournals.org/cgi/content/full/22/4/162>
 - **Pre-diabetes meeting:** The "1st International Congress on Prediabetes and the Metabolic Syndrome" takes place in Berlin from April 13-16. This has potential to be a fantastic meeting just based on the faculty, to say nothing of the clinical program and trial summaries/updates (DPP, Stop NIDDM, ACT NOW, TRIPOD, DREAM, NAVIGATOR). Book now ... <http://www.kenes.com/prediabetes/>
5. **Pfizer:** Pfizer had no new news on Exubera/inhaled insulin (nothing on US submission, nothing on studies, nothing on progress in Europe). We find this interesting given Sanofi-Aventis's extensive discussion (see below) of the tension between the two companies and the possibility of a change in the marketing agreement (and/or a legal battle as to whether or not Pfizer has the right to make a change unilaterally). This could ultimately develop into a pretty interesting brawl.
- **Pfizer discussed how neither a Bush nor Kerry presidency would change anything at the company**, which we felt was difficult to back-up from a perception perspective – the perception among many investors is definitely that things will be worse with Kerry in office although they did not acknowledge this. In our view, government policy is usually more about talk than action and we do not believe (unfortunately) that either administration is likely to change the game in a meaningful way.
6. **Merck: Merck expects Muraglitazar to be filed in the fourth quarter of 2004.** As a reminder, Muraglitazar is BMY's dual PPAR agonist that is positioned as beneficial both in terms of glycemic and lipid control. Bristol formed a co-promotion for this drug with Merck earlier this year.

- **Responding to a question on Muraglitazar**, the company said the threshold of necessary toxicity data had been passed. It was unclear whether they were referring to human toxicity studies as well as mouse studies but we assume both if they are about to file.
- **MK431, Merck's DPP-IV inhibitor**, is in Phase 3 trials and FDA submission is expected in 2006.

7. Sanofi Aventis:

- **Long acting insulin analog Lantus continues on a roll**, showing no signs of a slowdown, and it will be very interesting to see how growth changes once Novo's Levemir (detemir) is approved in the US. Lantus sales reached approximately \$285 million (224 Euros) worldwide for the third quarter, up 85% (up 67% in the US and 116% in Europe). The drug, now in its fourth full year on the market, appears destined to achieve a billion-dollar year, having reached sales year to date of 599 Euros YTD, or about \$775 million, using current exchange rates. The compound is now Sanofi's eighth largest drug. Regarding Novo's own long-acting insulin, Detemir, there's no word on that approval, though we must imagine 2005 at this point. Detemir showed some weight advantages at EASD, and real-world use will be very interesting to see! Aventis is enjoying longer-than-expected absence of a 24-hour insulin and marketing continues to be strong. Though Detemir is said to be doing well in Europe, Lantus growth there remains robust there as well.
- **Surprisingly, Sanofi-Aventis gave no update for Acomplia** (rimonabant), its anti obesity/smoking compound in Phase III. Currently there are seven Phase III trials that are part of two clinical development programs, described in more detail below.
- **Sounds like Sanofi plans to file rimonabant for approval in 2005**, making launch in 2006 possible. On the obesity side, we would view this as the leader – Sanofi's marketing muscle at EASD was out in full force, extremely impressive.
- **Amaryl, an Aventis oral antidiabetic drug**, achieved revenues of approximately \$200 million (161 million Euro), up 10%. This drug, which has been frequently marketed with Lantus as "one shot a day/one pill a day" therapy for type 2 patients, grew 12% in the U.S. and 6% in Europe.
- **A major focus on the call was inhaled insulin** and whether Pfizer wants to (or even legally can) change the agreement among Pfizer/Aventis/Nektar regarding the drug – lots of speculation has ensued now that Aventis is owned by Sanofi. Apparently Pfizer is debating whether to keep it or buy it (or possibly sell it to Sanofi, though this seems very unlikely). At present, each company has designated a banker to evaluate and value the product. Sanofi is in disagreement with Pfizer over whether the Aventis acquisition involves a change of control that gives Pfizer the option to buy the entire program from Sanofi-Aventis.
- **Sanofi was cagey**, and didn't appear overly eager on Exubera, noting that the company is "*considering its options.*" It refused to confirm that it really wants Exubera, noting that the compound is "*charming at first glance,*" but that they believe that market access/potential is far more questionable. To what extent is the European healthcare system ready/willing to pay for something that's "*essentially the same, but much more expensive*"?

8. Lilly

- **Diabetes care products achieved \$580 million in sales in Q304** compared to \$589 million in Q303 - down 1%. Year-to-date sales of \$1,936 million rose 4%. Diabetes care revenue decreased 8% in the U.S. to \$315 million, while international sales increased 7% to \$265 million.
- **Third quarter worldwide Humalog sales rose 10%** to \$265 million, while 3Q worldwide Humulin sales fell 8% to \$244 million.
- **Third quarter revenue for Lilly for Actos sales hit \$58 M** - down 13% - year-to-date sales for Actos hit \$324 million, up 2%. A new fiscal year for Actos agreement (w/ Takeda) starts in October; LLY expects sequential increase in sales for Q4.
- **Humalog is Lilly's #3 product by revenue**, Humulin is #5, and Actos is #11.
- **There were no questions from analysts on diabetes per se**, but considerable questions on restructuring plans. Lilly will be laying off some employees and realigning corporate priorities to achieve continued profitability in the face of what could be some rough years ahead on the sales front. This is not particularly surprising, as many large drug companies are doing the same thing right now – this is part of the feast/famine business cycle that seems to be natural for many pharmaceutical companies.
- **Lilly did make specific mention of Amylin** (and, by extension, exenatide) as an important part of the company's future. The context was basically a response to questions on how things would get any better, to

which LLY responding by addressing about restructuring (see above). Their response makes sense to us as this diabetes stalwart has, in exenatide, an extremely exciting compound – particularly compared to its current insulin products, which are under real competitive pressure. Price increases have helped in recent years, but are less and less likely, in our view, to be instituted broadly going forward.

9. **Novartis: There was little diabetes or obesity focus on Novartis' conference call**, but it was re-affirmed that filing of LAF-237 was still planned for 2006. No further details were given, but this is consistent with what we have been expecting. Interestingly, Novartis had an R&D set for November 30, 2004 but has canceled it. The release said, *"To release pipeline info closely linked to news flow, Novartis will replace the R&D day event scheduled for November 30, 2004, with several R&D updates beginning on Jan 20, 2005, coinciding with the reporting of full year results."* Although this most likely has nothing to do with LAF 237 per se, it sounded a bit odd.

10. Aradigm

- **As reported recently, all responsibilities for AERx** (Aradigm's inhaled insulin product) have been transferred to Novo Nordisk. Additional Phase 3 studies of AERx are apparently planned for 2005.
- **This agreement eliminates all milestones** between Novo and Aradigm. Novo has the right to explore alternative technologies for pulmonary insulin.
- **Novo has obligations** to move forward in *"timely fashion."* Aradigm will maintain sole ownership of IP.
- **Key questions for us are two:** first, how seriously is Novo in terms of taking over this technology, and second, what other technologies for inhaled, if any, is Novo considering?

Commentary: Times are definitely a'changing for many pharmaceutical companies. Patent expirations, generics competition, a dearth of new products, and fears of government brow-beating on pricing are all coming to a head to make life "interesting" for big pharma executives. Several companies have launched major restructuring efforts and few management teams appear glowingly optimistic at present. Thus, we might be approaching a cyclical trough. Then again we must note that diabetes care seems to be something of a "redheaded stepchild" for most pharmaceutical companies – companies don't want to talk about it, and analysts don't seem to want to ask about it. Curious, given that diabetes prevalence continues to grow at alarming rates and no companies have yet managed to come close to a magic bullet for the disease. Still, we think many interesting drugs and devices are just on the cusp and so we're staying very tuned.

-- By Stephen Simpson, Andrea Stubbs, and Kelly Close

11. **Medtronic 2004 analyst meeting:** Medtronic hosted its 2004 analyst day earlier this month; the attached reviews highlights relevant to its diabetes business.
- **Medtronic's analyst day was a full day showcasing its various businesses.** In the introduction, CEO Art Collins stressed that the company did not view itself as a conglomerate and emphasized that it saw its diabetes as the business with the highest growth potential. He also highlighted that Medtronic viewed diabetes as a highly under-penetrated market currently – one assumes this means pumps as well as sensors, although Collins didn't get into specifics. He did note the company's expectation that by 2009, diabetes and core neuro would be the company's second biggest business – by our count, it would have to hit \$4 billion in revenue to achieve this, assuming that CRM and spine grow at 15% per year.
 - Although that sounds like an impressive goal for a company that has the highest revenue in cardiovascular functions, it's important to note that core neuro/diabetes used to report as one segment and now report as two – so a bit odd to put them together again for the sake of a growth statement. Currently, core neuro/diabetes already represent the third biggest business, of five.
 - Fiscal 2004 revenue for diabetes hit \$560 million, up 18% from a year earlier.
 - Two thirds of its current revenue stems, the company said, from products that are two years old or less – the company is expert in lifecycle management, bringing out new products that leverage the old, etc.
 - Medtronic has set of goal of 20% growth for diabetes for some time and never quite achieved it. Ultimately, they projected high teens growth for next couple of years and 20% further out.
 - Collins mentioned that Medtronic is very committed to CareLink, which is its business to monitor remotely patients that have Medtronic cardiovascular devices. <http://www.medtronic.com/carelink/> -

- use of this technology in diabetes is an interesting idea, although remote monitoring would need some reimbursement on the diabetes front.
- McCaulley on Medtronic's Diabetes business:** Head of diabetes Jeff McCaulley led an extremely comprehensive look at its diabetes business. We were surprised at the level of detail overall; they hadn't given such specifics before. Notably, McCaulley characterized diabetes as the segment with the "most opportunity" within Medtronic – this is a big statement for a company known primarily for cardiovascular devices to make though for the entire industry, it makes sense, given how under-penetrated pumps are and how little patients with diabetes test their blood glucose, relative to what is optimal.
 - To start, McCaulley noted Medtronic's #1 market share in pumps. Of \$560 million in revenue in fiscal 2004, 23% was international revenue, or about \$129 million. They seem to have made good strides overseas in the past year, likely largely as a result of Disetronic's problems in the US – they undoubtedly have managed to leverage this overseas, even as they have experienced problems here in the US with recalls (e.g., 511, Quick Set Plus), none of which were mentioned.
 - McCaulley mentioned some notable statistics that helped educate the audience:
 - One-third of all children born today will develop diabetes⁴. Daunting, though we do point out, most of these children will ultimately develop type 2 diabetes, not the primary market for pumps currently, though this is a market that is growing, from a small base.
 - One-third of patients with diabetes have A1c of 9.5%+ -The more-often quoted 64% of patients with type 2 diabetes having an A1C of over 7.0 was not cited. Think of it – 33% over 9.5% - we try to spare the melodrama, but indeed, that's frightening.
 - McCaulley gave estimates on penetration of pumps into markets, including:
 - The type 1 US market is 23% penetrated – they used 1.0 million as a denominator, implying a total type 1 pump population of 230,000 currently;
 - The type 2 US market is 1% penetrated – they used 3.0 million as a denominator, implying that ~75% of all type 2 patients on insulin might be the market for a pump, which sounds high to us. This also implies a total type 2 pump population of 30,000 currently, which, again, sounds high at our end.
 - Worldwide, Medtronic estimated that the type 1 market is 8% penetrated, implying that 400,000 type 1 patients have insulin pumps, or 170,000 overseas. Again, at the risk of sounding like we have better sources than Medtronic – clearly, we don't - this sounds high to us.
 - Worldwide, Medtronic estimated that the type 2 market is "considerably less" than 1% penetrated. We believe probably fewer than 0.1% of "eligible" type 2 patients likely have the pump – all depends how one defines eligible. To quibble, we believe noting the number of type 2 patients on insulin is probably too simplistic.
 - McCaulley on Medtronic's growth strategy for diabetes:** We applaud these strategies – if serious focus is put on these strategies, it will be positive for the entire industry.
 - #1: Enhance and simplify therapy: Here, Medtronic specifically mentioned Internet and informatics – this is related to its Carelink business in cardiac rhythm management, where they've seen some good successes. Carelink in diabetes would leverage pump data for data capture, i.e., blood glucose data, patient logs, insulin dosages, "and more."
 - #2: Support large trials to demonstrate outcomes (for reimbursement and treatment expansion): Hurrah! We can't wait to see more of this – and we hope more randomized, controlled trials are coming, as again, this will help all patients because it will, if the trials are successful, make it easier for healthcare professionals to prescribe pumps and have them reimbursed. We hope that Medtronic also invests in education – as products become more complex, this is highly necessary, given poor reimbursement for education today.
 - #3: Expand indications: Here, they appear to be discussing expanding indications for individuals with type 1 and type 2 diabetes.
 - McCaulley on the path to the "artificial pancreas":** While we feel the term artificial pancreas is overused, we welcomed clarity of information and forecasts of pipeline products:
 - Expect full market release of Guardian in the third quarter (e.g., between November 2004 and January 2005.) This is the alarm product that was approved by the FDA in April.

⁴ K.M. Venkat, et. al. *Lifetime Risk for Diabetes Mellitus in the United States*, JAMA, October 2003; 290: 1884-1890.

- The PMA for Guardian RT was submitted in August. Expect Guardian RT (real-time) to be launched next year (FY 06). This is Medtronic's sensor, separate from the combined "augmented" sensor – pump, as we understand it. This gives them over one year for approval. We believe they are expecting, for the first go-round, an adjunctive label, rather than a substitute label, and thus are forging a different strategy than Abbott (see above). This is not surprising given the results of the DirecNet study published in *Diabetes Care* earlier this year. It did not appear, based on their study, that at this stage the CGMS was accurate enough at hypoglycemic levels, to warrant a substitute label.
- Expect launch of the Paradigm 515 and 715 later this year.
 - Differences from the 512 and 712 are "increased flexibility of bolus calculator and selectable action curves." No doubt, the latter refers to the unused insulin calculation. Increased flexibility of bolus calculator may mean more user-defined settings.
 - Management said this system should be fully upgradable to sensor-augmented system. This is an excellent goal, although we would prefer to see marketing based on current features rather than features promised in the future. We are sensitive about this because patients have been disappointed over the years in terms of over-promises – as have healthcare professionals. Medtronic has termed its "customer loyalty" program to allow for upgrade to most current model the Paradigm Pathway.
- Expect launch of the "sensor-augmented pump" in 2006 (unclear whether fiscal or calendar was meant, but we assume fiscal) – Medtronic clarified this is the "combination product," i.e., the integrated meter, sensor, and pump (the Paradigm Link Meter, Guardian RT, and Paradigm 522/722).
- Expect launch of the "open loop" in 2007. Very few details given on this topic.
- Expect launch of the "closed loop" in 2008. Very few details given on this topic, except that a first study testing algorithms for external closed loop would be done in southern California. A pediatrics study at Yale is also in the works, along with "other additional studies." Implanted closed loop studies are ongoing in France. We will be watching for data.
- **McCaulley on clinical studies:**
 - The first study McCaulley discussed was a sensor-augmented feasibility study.
 - 10 users
 - Study achieved full 1% reduction in A1c after 90 days. Average baseline A1C was 7.8% at start, and 6.8% at end.
 - Pump therapy studies: They stayed on this slide only briefly – basically seemed a quick summary of the notion that pump studies show better HbA1c results (data has actually been mixed – although the most recent 5-nations study at EASD was supportive of pumps. We'd like to see more pump vs insulin studies use Lantus, as we feel NPH is no longer a fair comparator, since it is used relatively infrequently.)
 - Plans for sensor-augmented trials: Medtronic said it would launch two trials. The first is regulatory – seven centers, 140 patients, six months. They said this would begin in the third quarter of fiscal 2005 – shortly! The second is called "Treat-to-Target", which appears to be a large outcomes trial to show superiority of pump versus either injections. Management mentioned that the goal of this study was to garner reimbursement. It is planned to be a big trial -- 25 centers, 600 pts, 1-year treatment, and 1-year follow-up. This should begin in the fourth quarter of fiscal 2005. It hopes to file this within the next year.
 - Economic studies: Medtronic is clearly at work on this front, which is critical. It estimates that \$3.1 billion in cumulative savings over ten years could be made if type 1's A1Cs were lowered to 7% or less on average. Source for such a calculation was not shown. For type 2 patients \$97B savings could be made if A1Cs were reduced to 7%. Offhand, this seems an incredible stretch, though clearly, we believe the economic arguments do exist.
- **Other:**
 - Some in-hospital data was discussed – Medtronic is clearly focused on this area as well and we view it as a very, very important area to watch. .
 - Growth drivers – smart pumps, deeper penetration, market exploitation, and hospital growth.
 - Analyst question: When will continuous model be approved for replacement of finger-stick tests? Management said that it would build data to go back and get progressive labeling/approvals. It is still "officially" regarding continuous monitoring as adjunctive to fingersticks. To us, the strategy appears to be to get FDA comfortable, get a foot in the door, and then gradually expand indications.

- Sensor reliability arose, and Clarke Error Grid was discussed. Medtronic said that improved accuracy, reliability, and longevity of sensors would help. It quoted 95-98% accuracy via Clarke Error Grid, and mentioned 16-17% with respect to prospective accuracy. We are very interested in watching how all continuous monitors will perform under the 'new' error grid, which incorporates accuracy as well as rate of change.

-- By Stephen Simpson and Kelly Close

12. **Fundraising news** – It was announced this morning that Pelikan Technologies closes \$29 million Series D financing round:

- Palo Alto-based Pelikan Technologies closes round led by Zurich-based Swissfirst Bank AG – the company has now raised \$46 million since its 2001 inception. Other current investors include HBM BioVentures, Mannheim Holdings LLC, and Heidelberg Innovation.
- Management expects the Pelikan Sun, Pelikan's lancing device, approved in late 2003, to be launched in spring, 2005. Distribution news for the lancing device is expected by late 2004 or early 2005.
- Management looks for work on the integrated device (lancing device plus blood glucose monitor) to continue throughout 2005 and now expects to launch the device in 2007. Four potential benefits of such a system have been characterized as less pain, less hassle factor, faster speed, and potentially better precision. Clinical trials are expected to begin in the US toward the end of this year.
- For more information on Pelikan products, see our story on the company from 2003 at this link. <http://www.closeconcerns.com/dcu/Company%20in%20Focus%20-%20Pelikan.pdf>
- No valuation information was available, apart from the fact that the round was an up round and that valuation was going "*the right direction*," according to Pelikan's Vice President of Finance, Patrick Nugent.

Odds and Ends

- **This Saturday, October 30, right after the Diabetes Technology conference** (www.diabetestechology.org) and right before ISPAD (<http://singapore2004.ispad.org/>), Close Concerns will have a small team walking to support the Juvenile Diabetes Research Foundation and ultimately, a cure for type 1 diabetes. If you would be willing to make a small donation on behalf of our team, to push forward potential for the cure (it's still forever off in our view but it's worth funding), we'd be very grateful. <http://walk.jdrf.org/walker.cfm?id=85867467> All contributions tax –deductible :>.

Appendix: More on Roche commercials:

So we couldn't possibly put this much in the regular newsletter about Roche Compact commercials, but truly this is a fascinating topic.

- These commercials are refreshing, featuring "real" patients, spotlighting them up front and close. Why do we like them? I (Kelly here) could write a book about it – I watched them over and over and over at AADE, just like I watched over and over LifeScan's outstanding *Live Life Without Limits* campaign a few years back (we think Roche has expertly borrowed some of the best ideas, but we applaud it, because the LifeScan campaign was incredibly well done.) We insist on taking the opportunity to share with you the language of the ads, because we like them so much, even though unfortunately, you really need to see them to understand the power:
 - Caucasian boy, ~12 years old: "*I work out. I hang out. I go out. I'm a ball player, a student, a musician. I test -- 6 times a day. I never let my friends down. I never let myself down. I am a friend. A brother. A diabetic. I am a diabetic ...and this is my meter...*" Announcer: "*The Accu-chek Compact System. Finger or forearm test. Faster results. The one with the drum.*" *Accu-chek. Live life. We'll fit in.*"
 - Latina woman: "*I'm a teacher. A teacher who speaks three languages. I am a sister, and a daughter who loves her family. I test. I test four times a day. I'm a runner. I'm a dancer. I'm a*

diabetic. I'm a diabetic. And this is my meter..." Announcer: "The Accu-chek Compact System. No strip handling. Finger or forearm test. Faster results. The one with the drum." Accu-chek. Live life. We'll fit in."

- Same Latina woman: "Corro dos millas al día. Trabajo. Cuido a mi familia, mi trabajo, a mi misma. Lucho por lo que deseo. Nunca me rindo. Me hago la prueba. Me hago la prueba 4 veces al día. Soy hija. Madre. Esposa. Soy diabética. Soy diabética... y este es mi medidor. Announcer: "El Nuevo sistema compacto de ACCU-CHEK. Sin necesidad de tocar la tira. Pruebas en el dedo o en el antebrazo. Resultados más rápidos. Accu-Chek. Vive la vida. Nosotros nos acomodamos."
- Okay, so John called me when he first saw it on BBC America – he liked the ad too, but he couldn't imagine how much I would like it. Luckily he had TIVO'd the first one he saw, which was the kid. So the kid is a cool kid –you'd be proud to be his parent, brother, or friend. That's great for a fellow patient to see. The kid has got it together – all the patients do in these ads, which represents one enormous level of appeal. Even though patients sometimes feel diabetes is running their lives and they think about it every 20 seconds, these patients seem pretty in control. Two, they seem to have *normal* lives. Three, they are "high performing" patients – rather than hiding from diabetes, they test frequently, and they all appear to be doing pretty well. They aren't saying it's easy, but they're obviously coping and it's appealing from a patient perspective.
- So (still Kelly here) I liked the ads so much I started watching BBC America every day, as I'd now heard there were three ads and I was hearing about them everywhere. BBC news seems way smarter than US news by the way! Anyway, I didn't see the others, but at AADE, they were playing continuously, and it was my favorite thing to go watch them. In addition to the two above, there was another one of another pretty-together woman – also quite appealing. I ultimately felt that the ads were probably great for Roche, but they weren't focused specifically on the Compact brand, i.e., they weren't a hard sell, which was nice.
- Ultimately, I'm sure these ads have been positive for the industry. Two of my friends, by the way, called me since the campaign was on ... "Are you testing six times per day?" How excellent is that – community awareness-raising through TV spending! While the cynical would call it a power sell, I can honestly say, if you know someone with diabetes (at least whose A1C is > 6.5-7.0), in my view they can really benefit by testing that much or more – and since the national average still hovers around 1.7 times per day, we've got a long way to go.
- Okay, almost done with the soapbox – there are two other really interesting element to these ads. First, all the actors (who are real patients) say "I am a diabetic ...". As some of you may know, some healthcare providers and patients urge that the word diabetic not be used as a noun, as some see it as insulting. We view Roche's response as an urge for people to call themselves whatever they like, and honest-to-God, move ON from this ridiculous language obsession and just move to better care. Okay, and the second thing – this appears to be pretty smart ethnic marketing. While some might say it doesn't represent what the true *average* Spanish speaking patient is like ("We don't all speak three languages," said one Argentinean indignantly), Roche seems to be thinking broadly about existing and potential targets to educate.
- In a word - bravo!

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Many thanks to Melissa Ford and Janet Ng for help in researching and writing this edition of *Diabetes Close Up*.

Diabetes Close Up is a newsletter highlighting notable information and events related to selected companies with diabetes/obesity businesses. This newsletter is put forth as an unbiased commentary on the industry. If you have any suggestions or comments regarding content, please contact info@closeconcerns.com. If you would like to 1) unsubscribe; 2) add a name to the DCU mailing list; or 3) offer any suggestions or comments regarding content, please write to info@closeconcerns.com.

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