

CLOSE CONCERNS

**Diabetes Close Up, V2, #11
July 10, 2003**

Greetings! It's a beautiful day in Oahu, where my husband John and I are on an extended summer holiday. I hope this finds you all well. A few items on the diabetes docket that I thought might interest you:

- 1. ABT reported this morning – ww reported MediSense sales increased approximately 3% year over year.** A backorder and tough comps represent the primary reason for the relatively flat sales – a backorder on G2 strips representing the primary factor - and forecast better performance for 3Q with normalized growth in 4Q.
 - 2. MDT/BD pump/meter combo approved** - the Paradigm 512 and the Paradigm Link Blood Glucose Monitor, developed with BD, received FDA clearance on July 7.
 - 3. Recent submissions of note** from Amylin and Aventis
 - 4. Kraft Cracks**
 - 5. More focus on obesity – July 9/10 NY Times~ Journal of Clinical Endocrinology and Metabolism**
 - 6. Upcoming diabetes/obesity-related earnings reports**
 - 7. Upcoming diabetes/obesity-related conferences**
- Appendix: More thoughts on integrated pumps/monitors.**

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1. ABT reports:

- a. **As noted above, Abbott MediSense sales reached \$128 million in the second quarter, up a muted 3% reported - excluding the FX benefit, sales dropped 4%.** US sales fell 1.4% to \$50 million and reported int'l sales rose nearly 6% to \$78 million (excl. FX, int'l sales dropped 6%).
- b. **As noted above, a backorder on G2 strips caused some weakness in 2Q;** Abbott expressed confidence that manufacturing issues are now resolved. Assuming the back orders come in and that 3Q demand doesn't drop (increased competition still poses some concern though market growth will continue to help all), it sounds like double-digit growth for the quarter is in the bag.
- c. **Having spoken to the company, it also sounds like double-digit growth for the year is doable as well.** We have now pegged our 2003 forecast in a range of \$540-\$550 million, which represents 10-11% growth, following 8% and 9% increases in 2002 and 2001, respectively.
- d. **If a “product availability” situation is at hand, good for Abbott:** While I had suspected revenues might be lumpy because MediSense's 1Q results of 11% growth were better than much of the industry including well-entrenched competitors, the G2 strips backorder situation cited by management appears to represent the main reason for the sales weakness. Yes, if a “product availability” situation is at hand, good for Abbott – better than a demand problem, which some expected given MediSense's relatively more restrained marketing spend and absence of recent new products. We will look for the backorder to emerge and will continue to monitor IMS data.
- e. **Although Abbott didn't show new products at the ADA, I would still look for continued strip innovation¹.**

¹ Big-time tangent - I think Abbott has among the more accurate strips on the market, but interestingly, it has never reaped full credit for this (nor has TheraSense) in my view – the market seems to believe that once the FDA approves something, it's 100% accurate, which isn't true at all! As clinicians continue to focus on tighter control, more manufacturers may tighten controls on this front – I think Abbott has among the least work to do here. Currently, standards require accuracy within 20% at most levels – that means that a score of 90 might actually be 72 or 108 – that doesn't sound like a big difference (though to hyper-intensively managed Type 1s it is – it could be the difference of a 6.5 or 7.0 A1C) but the point is made more clear with errors at higher levels – for example, a score of 200 might actually be 160 or 240 – ouch. At 160, I'd take a 1 unit correction bolus, but at 240, I'd take two – plus units.

2. MDT/BD pump/meter combo approved: Medtronic announced FDA approval on July 7 for its new wireless blood glucose monitoring and insulin pump combination system – the Paradigm 512 and the Paradigm Link Blood Glucose Monitor, developed with BD. Via wireless technology, the Paradigm Link monitor automatically sends a blood glucose reading to the Paradigm 512 insulin pump, which then automatically suggests action for pumping based on the result. The new systems aim to enhance both glucose control as well as broader quality of life by simplifying the blood glucose monitoring and insulin dosing processes as well as making them more accurate – while I haven't had an opportunity to test the system, I should say that integrated pump/meters have certainly prompted some excitement on the patient front and I would expect all insulin pump leaders to have this functionality within the next year or so². In addition to the bolus wizard, the pump also calculates unused insulin – a feature that may reduce hypoglycemia further³. See appendix for additional thoughts on this new product.

3. Recent submissions of note:

- a. **Amylin submits Symlin, publishes promising Exenatide data:** Amylin submitted data on Symlin to the FDA in late June; PDUFA guidelines would suggest we could hear something on the approval front by year-end about this new hormone (first new drug for Type 1s since insulin) that is drawing some keen interest from insulin users. Notably, Amylin also announced yesterday that positive data on its Type 2 compound exenatide was published in July's *Journal of Clinical Endocrinology and Metabolism* – clinicians with whom I spoke at the ADA say the drug could revolutionize treatment for Type 2's – very welcome news for patients. Stay tuned ~
- b. **Aventis: Announces Regulatory Submission** for rapid acting analogue insulin glulisine (EU and US). Glulisine is a recombinant human insulin analogue that has a more rapid onset and a shorter duration of action than human regular insulin – it will compete with Lilly's Humalog and Novo's Novalog. They are aiming for a label that will include pump usage – Novalog is currently the only insulin approved for pump use. Analogs have been a huge success and I actually who uses regular insulin anymore – Lilly and Novo have clearly benefited from the migration to analog insulins. The approval of this product will be important for Aventis, as it'll add a valuable rapid-acting insulin to its arsenal, which was bolstered substantially with the addition of basal insulin Lantus, which has been a runaway success since its introduction in 2001.

4. Kraft Cracks – Obesity problems have become truly mainstream - huge headlines in *USA Today*, the *Wall Street Journal* and the *New York Times* trumpeted Kraft's recent landmark announcement that it would introduce smaller portion sizes, develop healthier, more nutritious products (less sugar and fat content), and importantly, would eliminate in-school marketing to children (marketing that has probably been among the most lucrative in the company's history). Additionally, Kraft will develop new standards to enhance the overall nutritional content of its foods and as noted, significantly change its product marketing practices. All a way of saying the behemoth would do its part to begin to address the obesity problem that threatens to spread truly out of control.

- a. **The food manufacturer announced that it would reformulate many of its products and make other strides to combat the current rise in obesity among Americans** (and the world) on July 2 – no doubt the announcement timing wasn't accidental – the early stories appeared just before a holiday where many Americans typically gorge on various, shall we say, less healthy food items.
- b. **In a move that foreshadowed the FDA's decision yesterday to require companies to list levels of trans fatty acids in products by 2006 (www.fda.gov/oc/initiatives/transfat/), Kraft said it would remove trans fatty acids from Oreo cookies** – nothing is sacred any longer, one infers. This is great news for consumers – though it'll be interesting to see how long this takes. McDonald's said last year it would work to remove trans fatty acids from its products – to date, it

² Patients typically replace insulin pumps every 4-5 years.

³ Most short-acting insulin remains in the system about four hours. If a patient boluses more than once in a four-hour period (typical with more post-prandial testing), the tendency to overcorrect increases – the patient often forgets (in a fit of seeing 200 on the meter) that he or she still has other insulin working in the body. This new pump calculates the unused insulin for the patient, a nifty feature that actually first appeared with the Deltec pump, and which patients appear to find valuable. Deltec also pioneered another version of the bolus wizard; one advantage of Medtronic's wizard is, however, that it can use multiple insulin to carb ratios while Deltec uses only one. (Insulin to carb ratio refers to the amount of insulin required to process a given number of carbs. 1:15 is a common ratio, though it is not the right ratio for all patients. Many patients find that the insulin to carb ratio changes throughout the day.)

- has taken them out of chicken but that's it. The initiative to remove trans fatty acids from fries is now "on hold" as the company continues to search in vain for a new formulation.
- c. **As a piece in this morning's *New York Times* ("Foodmakers Trim Fat as Lawsuits and Regulations Loom" - www.nytimes.com)** notes (David Barboza who covers the obesity beat for the *Times* is doing a fantastic job with this issue), **Kraft's parent company is tobacco giant Altria** (remember Philip Morris? Right, same company). Altria has paid out stacks of money in tobacco lawsuits and clearly doesn't want to go through a similar series of lawsuits/settlements. Interestingly, the total cost of obesity to the healthcare system in the U.S. was pegged at around \$70 billion annually at the recent AACE meeting in San Diego; this is close to the total healthcare system cost of tobacco, estimated at just under \$80 billion. Lawsuits and settlements have totaled in the hundreds of billions. Quote of the day from this piece: "*I wouldn't say we're part of the problem,*" said Steven Anderson, president of the National Restaurant Association, which represents big outlets like McDonald's and Burger King, as well as thousands of other restaurants. Please.

5. More focus on obesity:

- a. **There was a fantastically interesting and without being too dramatic, actually terrifying piece in yesterday's *New York Times* (also by Barboza) regarding obesity in youth in New York City ("Obesity on the Rise in New York Public Schools", 6.9.2003) www.nytimes.com. Importantly, this is indicative of the nation's obesity problem in my view, not just NYC.** Among other stats, the article noted that over 40% of NYC elementary public schoolkids are overweight and fully 24% are obese⁴. The problem looks worst for racial minorities excluding Asians; in the survey, obesity rates were 14 percent for Asians, 16 percent for whites, 23 percent for blacks, 31 percent for all Hispanics and 36 percent for Hispanic boys. Health Commissioner Thomas R. Frieden's remark said it all – that the results were nothing less than a calamity in the making – a future wave of heart disease, diabetes and a raft of other ailments. "*What's changed is the increased sedentary lifestyle, the supersizing fast-food, video game culture, and it's leading to a real epidemic,*" he said.
- b. **Small study, interesting results - *Diabetes In Control*** recently cited a *Journal of Clinical Endocrinology and Metabolism* piece (April 2003) that showed that in a national study, women lost more weight on a lower-carb diet than on a lower-fat diet, even when the calorie load was the same. The lower-carb diet group lost more weight (18 pounds) and more body fat (10.5 pounds) than the lower-fat diet group (8.5 pounds and 4.4 pounds, respectively). Study subjects were informed that the intent of the study was not weight reduction and were not included if they expressed a desire to lose weight. Conducted over 4 months, the study took place at the General Clinical Research Center (GCRC) of the University of Washington. Although the study was small (n=18), this has interesting implications for dietary goals. **Key Findings:**
- Consumption of a low-fat, high-carbohydrate diet led to significant reductions in food intake and body weight without an increase in AUC-leptin.
 - Leptin, a hormone, seems to have in inverse relationship with appetite (i.e., as leptin levels decrease, appetite increases and vice versa). For example, people with genetic mutations that inactivate leptin or its receptors have an insatiable appetite and eventually become obese. The results of the study also suggest that dietary fat restriction enhances leptin sensitivity.

6. Upcoming earnings reports with implications for diabetes/obesity markets:

- JNJ – Tuesday, July 13, 8:30 am EST
- THER – Thursday, July 24, 5:00 pm EST
- BDX – Thursday, July 24, 8:30 am EST
- AMLN – August, date/time TBD
- IMDC - TBD
- MDT – Week of August 11 (estimated); annual meeting occurs August 28

⁴ This is based on a survey of 3,000 kids K-5th grades conducted in May by the Department of Health and Mental Hygiene and the Department of Education

7. Upcoming diabetes/obesity – related conferences:

- a. **AADE:** August 5-9, Salt Lake, www.aadenet.org - last day to get early bird discount is July 11.
- b. **EASD/IDF:** August 24-29, Paris, www.easd.org - last day to get early bird discount is July 11.
- c. **NAASO Annual Scientific Meeting:** October 11 – 15, Ft Lauderdale, www.naaso.org/meetings/
- d. **Canadian Diabetes Association:** October 15-18, Ottawa, Canada. www.diabetes.ca
- e. **American Heart Association:** Diabetes symposium led by the great Dr. Steve Marso: November 9, Orlando – www.scientificsessions.org.
- f. **Diabetes Technology:** November 6-8, San Francisco. www.diabetestechology.org

APPENDIX

Five thoughts on Medtronic's new gizmo

1. How easy the new system is to operate will be key to watch; Animas made huge strides with insulin pumps by simplifying the process and on this front, it's my view that Medtronic has been playing catch up. Some patients have voiced issues on the Medtronic service front; this continues to bear close monitoring as this product will require some education – possibly significantly more phone calls to Medtronic, at least in the early days. Recent added competition for Medtronic has come from Deltec; Deltec's first entry into the pump market has drawn positive reviews and provided unexpected competition due to new features (bolus estimator, unused insulin feature) and small size. If the Medtronic product works well with few errors, the patient word-of-mouth will quickly emerge – if it doesn't, this will come through as well. I'll be monitoring the boards ~

2. Reservations aside, it does appear that Medtronic now has a better product to offer; the integrated glucose meter is a differentiated concept that I suspect will appeal to at least a certain subset of patients.

- **Here's why some would find integration a positive:** while the pump and meter aren't in an "all in one" package at this point (TheraSense and Deltec will be the first to offer this with their combined product, now at the FDA), I reckon the integrated product will make insulin dosing easier and likely more accurate as well. How's that? Right now, here's the process for pump patients: 1) one typically checks blood glucose; 2) calculates (often with significant rounding error) how far off one is from target; 3) calculates what insulin is needed to cover the gap (often with significant rounding error); and 4) boluses⁵.
- **What this product will do is, using preset targets, preset insulin sensitivity levels⁶, and insulin-to-carb ratios, calculate what insulin bolus a person needs.** What is good about that?
 - It's better to have a machine do the math because it'll be more accurate⁷ - the integrated system can improve insulin dosage accuracy merely by reducing reliance on mental calculations of insulin dosage;
 - It's nice to have the machine do the math, because one simply tires of doing it multiple times per day (any time one eats or takes a correction bolus).

3. One interesting potential implication -pump patients are among the most frequent blood glucose monitoring testers – the integrated device may be so easy that they start to test even more frequently. Pumpers are a relatively small part of the market – 15-20% of Type 1's – but they account for a higher share of profits⁸ and represent quite valuable customers⁹ – the most well entrenched competitors may be at risk for losing some valuable customers on this front, at least in the short term while competition catches up. Pumpers are frequent testers because they have to be - pumps by design use only short-acting insulin,

⁵ Unless their score is 80-120 and they have no plans to eat – take it from me, this almost never happens

⁶ That is, the rate at which blood glucose is reduced resulting from one unit of insulin. 1:50 is a common ratio, though it is not the right ratio for all patients. Many patients find their insulin sensitivity changes throughout the day, and it is often highest in the early morning, creating what is known as the 'dawn phenomenon'.

⁷ Many pump patients currently bolus to the nearest half unit or unit; the bolus estimator (in both the Deltec and Medtronic pumps) makes accurate dosing easier.

⁸ I've done some preliminary work on this and have a simple spreadsheet with my view of the market – let me know if you'd like this.

⁹ Currently, I divide pumpers into "intensive" (4x day/testers) and "hyper-intensive" (8x day/testers). The main difference is that intensive testers mainly test before all meals and when they fear hypoglycemia, while hyperintensive testers typically test before meals as well as monitoring post-prandial levels – they may check at the 1-hour or 2-hour mark following meals – as well as in cases of hypoglycemia.

which raises the risk of ketoacidosis in the case of hyperglycemia. I suspect this new device – if the reviews are good and patients like it – will result in patients that test more frequently – particularly post-prandial testing¹⁰ and other testing between meals. Good news for BD – though this may take awhile to result in real sales since typically insurance companies approve new pumps only every 4-5 years. The Medtronic “upgrade” program bears watching – the company may make it easier for patients to migrate to the new product faster, but no real view on this yet. It will obviously be key for BD to improve its managed care coverage – but this new product may be the incentive to get patients to request coverage of BD’s Logic strips.

4. On that front, I wouldn’t expect the competition to stand still for a moment. We saw the TheraSense/Deltec product at the ADA – elegant, small, all-in-one pump and meter. There have been questions on the Deltec service front – primarily that it’s an unknown factor - and the company should benefit from having TheraSense behind it as the Alameda company’s reputation for service is very strong. Too, Animas has received fantastic reviews for its current pump – in fact, the introduction of their pump was what prompted competitors to innovate faster, in my view, just to keep up – and this company will also continue to innovate. I look forward to seeing what is released next! Disetronic is on the sidelines, stemming from an FDA warning prohibiting shipping pumps in the US until further notice (to call a spade a space, I don’t have enough data for a real view on how long this will last but I’ve heard estimates ranging from six to eighteen months) which is probably helping all competitors a bit, though Disetronic didn’t have a strong business in the U.S. to start. The real question is what is happening to Disetronic demand in Europe – Medtronic would be the one that would probably mainly benefit there and I would assume the word is out on the US troubles for Disetronic.

5. Final word - I’m eager to see outcomes on the integrated pumps/meters: Can patients improve blood glucose management with this new tool? I’m positively disposed, and believe that this will prompt even more industry innovation – always great for the patient. Stay tuned ~

Diabetes Close Up is an occasional newsletter that highlights notable goings-on related to selected companies with diabetes/obesity businesses. This newsletter is put forward as an unbiased commentary on the industry. If you have any suggestions that you think should be included, please contact info@closeconcerns.com. Many thanks!

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¹⁰ A recent study (Arch Intern Med 2003 Jun 9;163(11):1306-16) showed that isolated postprandial hyperglycemia (2-hour postprandial glucose level >140 mg/dL) and *normal* hemoglobin A1c (<6.1%) were associated with a two-fold increased risk of death stemming from cardiovascular disease. What does this suggest – I think it is just another sign we need MORE frequent testing. Those that have 6.0 A1Cs may have their collective head in the sand ~.