CLOSER LOOK

MEMORANDUM

4Q17 and 2017 Diabetes and Obesity Industry Roundup - Industry tops $50 billion in 2017, with GLP-1s driving 52% of growth, SGLT-2s driving 23%, CGM driving 18%; Insulin flat in the face of pricing pressure; Pumps and BGM decline - April 16, 2018

Executive Highlights

- **Overall industry:** The diabetes industry spanning major branded drugs and devices (not including generics) grew 6% YOY (!) in 2017 to a record-high $50.3 billion in 2017, up from $47.4 billion in 2016, a year that saw 4% YOY growth. The industry showed similar single-digit growth in 3Q17 (+7% YOY to $12.6 billion) and 4Q17 (+7% YOY to $13.4 billion). This positive performance follows 5% YOY industry growth in 1Q17, 3% in 2Q17 - it's incredible to see the field growing faster from a higher base. Ultimately, we were a bit surprised to see this. While we have realized that GLP-1, SGLT-2, and CGM are propelling strength in the field, we've also written all year about slowdowns in insulin and blood glucose monitoring. All in all, we view 2017 as an extremely strong year for the diabetes industry, compared to a 4% YOY rise in 2016 and flat overall sales in 2015. We're looking ahead to see what concerns there will be: In addition to some generic entries for certain drug classes, we also expect continued US pricing pressure. That said, expanding competition should actually help the field, and we don't envision many regulatory hurdles, etc. In 2018, we look for continued strong performance from the main growth drivers.
- **Share of growth:** By our calculations, GLP-1 agonists were once again the primary growth driver for the overall diabetes industry. Three therapy/technology classes - GLP-1, SGLT-2, CGM - accounted for 93% of industry growth in 2017 - nearly all of it! This compares to 85% in 2016 and 99% (SGLT-2s drove 55%) in 2015. This is the first time we've included basal/GLP-1 fixed-ratio combinations in our roundup, and as a result, this class drove 5% of growth according to our model (we will be assigning each "half" to the respective area of GLP-1 or basal insulin in our next iteration). DPP-4 inhibitors and insulin pumps each contributed a small share of growth in 4Q17 (14% and 2%, respectively), but otherwise, all categories were either flat or declined in full year revenue. Notably, because DPP-4 inhibitors are such a large revenue category, 7% YOY growth in 4Q17 led to the appreciable 14% share of growth. As a class, DPP-4s contributed a 5% share of growth in 3Q17 with a 2% YOY climb in sales.
    - **GLP-1 as a class drove a whopping 52% of growth in 2017**, while accounting for only 13% of total industry revenue ($6.5 billion sales rising 32% on the year). GLP-1 agonists drove 38% of industry growth in 3Q17 ($1.6 billion sales reflected 13% of industry revenue) and 46% in 4Q17 ($1.9 billion sales reflected 14% of industry revenue), somewhat lower than we saw with 55% and 57% in the first two quarters of 2017, but obviously still very strong.
    - **SGLT-2 inhibitors contributed a 23% share of growth in 2017**, according to our model; the market grew 24% YOY to $3.5 billion, which represented 7% of the entire diabetes industry. Market growth for SGLT-2s accelerated somewhat in the second half of the year - 1Q17 and 2Q17 showed only 18% and 20% growth, respectively, while 3Q17 and 4Q17 growth came in at 35% and 23%. In line with this, SGLT-2s drove a higher share of industry growth in the second half of the year: 30% in 3Q17 ($935 million sales reflected 7% of total revenue) and 17% in 4Q17 ($1 billion sales reflected 8% of total revenue) vs. 16% and 21% in 1Q17 and 2Q17, respectively.

    - **CGM drove 18% of overall industry growth in 2017** (worldwide sales of $1.7 billion grew 46% YOY) - the class drove 15% of industry growth in both 3Q17 and 4Q17. This was actually a slight downtick from the record 18% and 20% share of growth in 1Q17 and 2Q17, respectively, which reflects larger growth in other areas of diabetes in 2H17, as the CGM category accelerated in the second half of 2017.

- **Diabetes therapy:** The GLP-1 class continued to soar in 2H17, with 25% YOY growth in 3Q17 (to $1.6 billion), 38% YOY growth in 4Q17 (to $1.9 billion), and 32% YOY growth for the full year (to $6.5 billion). Notably, GLP-1s are climbing faster from a higher base vs. SGLT-2s, which grew 24% YOY to $3.5 billion in 2017. Boosting SGLT-2 sales is the new CV indication for Lilly/BI's Jardiance, but on the flip side, FDA added a black box warning for amputations to the Invokana (J&J) label. This push-and-pull is muting what could otherwise be much more dramatic growth for the SGLT-2 inhibitor class. The injectable insulin market was flat at $21 billion in 2017 - basal insulin analogs experienced modest decline (-4% YOY to $9.9 billion) while mealtime insulin analogs experienced modest growth (+4% YOY to $8 billion). Next-gen basal insulins, including Novo Nordisk's Tresiba and Sanofi's Toujeo, grew 57% YOY to $2.1 billion in 2017 and we see both driving considerable growth ahead. Insulin offers one example of US pricing pressure, since US sales fell 3% YOY in 2017 while, remarkably, OUS sales grew 8% (of course, it is challenging to know if this US decline is price only or "volume" or "mix" or both). DPP-4 inhibitors were flat for the full year at just under $10 billion ($9.7 billion) - basal insulins are the largest class, still, by just a hair. Basal insulin/GLP-1 fixed-ratio combinations posted $142 million in their first year on the market. While this seems (and, let's face it, is) underwhelming, we have the impression that there is a great deal of inertia from medical systems to start patients on combinations; as well, while Soliqua is priced on par with standalone GLP-1 agonists, Xultophy is considerably more expensive both in the US and internationally, as we understand it. For drugs that had such great RCT results, it is distressing to see the uptake in these early days (Xultophy sales for 2017 were $112 million while Soliqua's were $30 million).
- **Diabetes technology:** For the first year in our model's decade-plus history, CGM was the only tech category to grow in 2017: we estimate pooled CGM sales of ~$1.7 billion grew by nearly 50% YOY, a record high for the category. By contrast, we estimate that pooled "Big 3" (Abbott, J&J, Roche) BGM sales of $4.3 billion declined 2% YOY, while pooled pump sales of ~$2.2 declined by 4% (as always, there are some estimates here). The marked CGM growth is a testament to international momentum (driving ~70% of the category's growth for the year, from a low base of about $1.0 billion), product improvement, global reimbursement wins, new trials and real-world data, and enthusiasm for the Beyond A1c movement and moving CGM to standard of care. BGM continued on its downward slide from 2011, reflecting continued devastation of competitive bidding and other pricing/competitive pressures (with some potentially positive momentum in international). It was a challenging year in pumps for Medtronic, and especially for Roche (discontinued sales in the US) and Animas (closed its doors); these declines were offset by a phenomenal 2017 for Insulet (driving 86% of the pump category's growth) and a strong 2H17 for Tandem and strong start in 2018 (the company recently pre-announced a positive 1Q18). Where will we see the greatest innovation in BGM moving forward?
- **Obesity:** Pooled sales from all major branded obesity drugs (Novo Nordisk, Orexigen, Vivus, Arena/Eisai) grew 54% YOY to $559 million in 2017, from a base of $364 million in 2016. Novo Nordisk's Saxenda generated nearly $400 million of these sales! Saxenda drove 77% of this growth, by our calculations, and captured 71% of whole class sales in 2017 ($394 million revenue grew 63% YOY). Orexigen's Contrave was shaping up to be another potential bright spot in this otherwise dim market (though nothing on the order of Saxenda), but the company recently filed for bankruptcy, partly highlighting tough commercial challenges for obesity products (though the company also had other challenges).

Based on financial results from the nearly 30 public companies that we regularly track, this diabetes/obesity industry roundup provides a bird's eye view of important trends in 2017, with a specific focus on 3Q17, 4Q17, and 2017 overall. We also include key details on each major drug class and device category.

This report is divided into four sections: (i) overall industry highlights; (ii) diabetes therapy; (iii) diabetes technology; and (iv) obesity. Within each section, we analyze sales performance, share of growth, and provide graphs with current and historical trends. Please note that in many cases, the data we've used for our analysis reflects our best estimates, since a number of companies don't disclose financial information in great detail. We've made the basis of our assumptions clear in the text below, but we recognize that a number of the estimates may be meaningfully different from the "actual" that is not known! If you have opinions on how an estimate could be improved, please don't hesitate to reach out and let us know.

Table of Contents

Diabetes Technology

BGM

"Big Three" BGM 2017 Estimated Sales of $4.3 Billion Decline 2% YOY; Two Consecutive Quarters of International YOY Growth

CGM

Worldwide sales of ~$1.7 billion in 2017, rising 46% YOY; 1st ever quarter crossing $500 million! OUS sales drive ~70% of category growth in 2017

Insulin Pumps and Delivery Devices

Sales Down 4% YOY on Challenging Year for Medtronic, Animas and Roche Exits; Strong 2017 for Insulet (86% share of category growth!) and Tandem

US AID Pipeline and Timing

International AID Pipeline and Timing

Obesity

Obesity Drug Sales Climb 54% YOY to $559 Million in 2017, Driven by Novo Nordisk's Saxenda (77% Share of Growth); Orexigen Bankruptcy Casts Shadow

Overall Industry Performance

Diabetes Industry Summary for 2017

Drug or Device Class	Total Sales in 2017 (billions)	YOY Growth	Share of Total Industry Revenue	Share of Industry Growth
Insulin (Basal + Rapid-Acting + Human)	$21.1 ($9.9 + $8 + $3)	0% (-4%, +4%, -5%)	42%	0%
DPP-4 Inhibitors	$9.7	0%	19%	0%
GLP-1 Agonists	$6.5	+32%	13%	52%
SGLT-2 Inhibitors	$3.5	+24%	7%	23%
Basal Insulin/ GLP-1 Combos	$0.14	--	<1%	5%
BGM	$4.3	-1%	9%	0%
Insulin Pumps	$2.2	-4%	4%	0%
CGM	$1.7	+46%	3%	18%
Other (BD)	$1.1	-2%	2%	0%
Total Diabetes Drug + Device Industry	**$50.3**	**+6%**	**100%**	**--**

Diabetes Industry Summary for 4Q17 and 3Q17

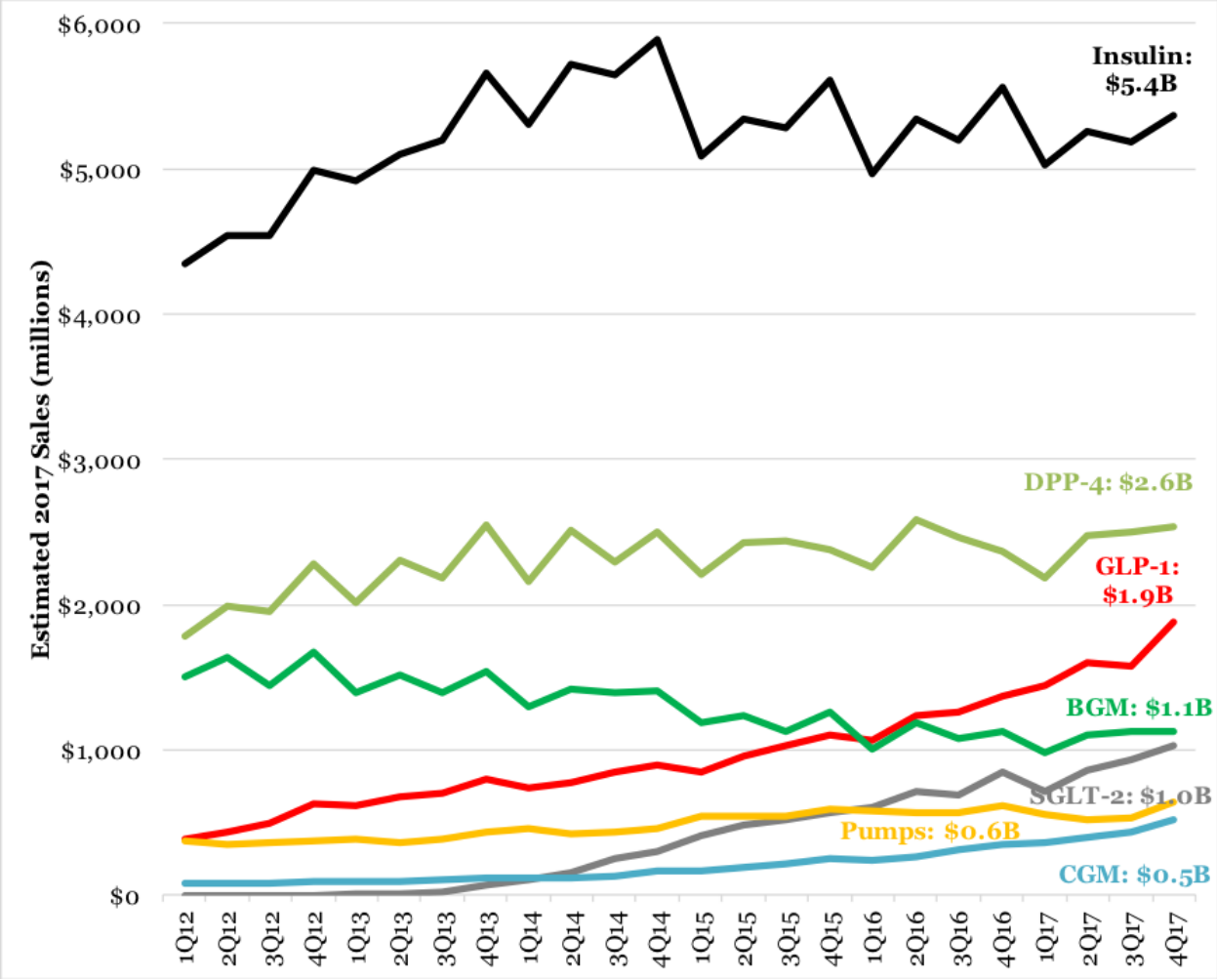
Drug or Device Class	Total Sales in 4Q17 (3Q17)	YOY Growth in 4Q17 (3Q17)	Share of Total Industry Revenue in 4Q17 (3Q17)	Share of Industry Growth in 4Q17 (3Q17)
Insulin (Basal + Rapid-Acting + Human)	$5.4 ($5.2)	-4% (0%)	40% (41%)	0% (0%)
DPP-4 Inhibitors	$2.5 ($2.5)	+7% (+2%)	19% (20%)	14% (5%)
GLP-1 Agonists	$1.8 ($1.6)	+38% (+25%)	14% (13%)	46% (38%)
SGLT-2 Inhibitors	$1.0 ($0.9)	+23% (+35%)	8% (7%)	17% (30%)
Basal Insulin/ GLP-1 Combos	$0.05 ($0.04)	--	<1% (<1%)	5% (5%)
BGM	$1.1 ($1.1)	0% (+4%)	8% (9%)	0% (6%)
Insulin Pumps	$0.64 ($0.53)	+3% (-7%)	5% (4%)	2% (0%)
CGM	$0.51 ($0.43)	+46% (+41%)	4% (3%)	15% (15%)
Other (BD)	$0.28 ($0.28)	+4% (+6%)	2% (2%)	1% (2%)
Total Diabetes Drug + Device Industry	**$13.4 ($12.3)**	**+7% (+7%)**	**100% (100%)**	**--**

Diabetes Industry Sales Climb 6% YOY, Surpassing $50 Billion in 2017; Whole Industry Grows 7% YOY in 3Q17 ($12.6 Billion) and 4Q17 ($13.4 Billion)

- **The diabetes drug and device industry grew 6% YOY in 2017 to $50.3 billion (from a base of $47.4 billion in 2016), hitting a significant milestone in >$50 billion annual revenue.** According to our analysis, which encompasses major branded drugs and devices (excluding generics), the industry grew 7% YOY in both 3Q17 (+1% sequentially) and 4Q17 (+6% sequentially), reaching all-time highs of $12.6 billion and $13.4 billion, respectively. This follows 5% YOY growth in 1Q17 to $11.5 billion and 3% YOY growth in 2Q17 to $12.5 billion, making 2017 overall a very strong year for diabetes product sales. Wow!
    - **For comparison, industry revenue rose 4% YOY in 2016 (to $47.4 billion) and was flat in 2015 (at $45.5 billion).** The last time the diabetes industry saw YOY growth as high as 7% was in 2014 (+7% from $42.5 billion in 2013 to $45.3 billion in 2014), driven by the emergence of SGLT-2 inhibitors and a very strong insulin market. Notably, 2014 was the end of the high-growth years for basal insulins Lantus and Levemir - declining sales from these major franchises (especially Sanofi's flagship Lantus) has been a substantial headwind for the insulin market, and in effect, has slowed overall industry growth since 2015 although the strength in GLP-1 and SGLT-2 inhibitors and CGM has offset this. Indeed, while we view 2017 as positive on the whole, there were definitely weak points within the $50+ billion industry, including Lantus and Levemir, human insulin (-5% YOY), BGM (-1% YOY), and insulin pumps (-4% YOY). The "next-gen" basal insulin class (Toujeo, Tresiba, plus Soliqua and Xultophy) offset weakness in Lantus and Levemir, and CGM sales offset BGM (the category together grew); insulin pump weakness was

weakness. Notably, this is the first time we've included basal insulin/GLP-1 fixed-ratio combinations in our roundup, now that Sanofi's Soliqua and Novo Nordisk's Xultophy both have a full year of reported revenue. This combo class contributed a ~5% share of growth to the industry in 2017, simply because it didn't exist on the market in 2016 (Soliqua was launched in early January 2017, and although Xultophy was first-to-market in Europe, it wasn't launched in the US until May 2017, plus Novo Nordisk didn't break out Xultophy sales until 1Q17). Although we don't consider the ~5% share of growth particularly impressive - in fact, with all the clinical hype surrounding basal/GLP-1 combos (superior glucose-lowering, weight loss, a milder side-effect profile), we expected higher volume/sales early on - we also had heard that physician inertia would be at least an initial problem for this field. Reimbursement is another notorious obstacle for diabetes drugs approved late in the year and launched shortly thereafter, due to timing of the payer contracting cycle, so we're hopeful that Soliqua and Xultophy will gain more commercial traction in 2018. That said, there are other challenges to uptake for fixed-ratio combinations as well, discussed below. Read on for our in-depth analysis of each therapy and device class.

Overall Industry Revenue (1Q12-4Q17)



GLP-1 Agonists, SGLT-2 Inhibitors, and CGM Drive Almost All Industry Growth

- **GLP-1 agonists were the primary growth driver for the diabetes ecosystem in 2H17. By our calculations, the class contributed a remarkable 52% share of growth in 2017, with**

pooled sales of $6.5 billion reflecting only 13% of total industry revenue. In 3Q17, GLP-1s drove 38% of growth with $1.6 billion sales reflecting 13% of industry-wide revenue, and in 4Q17, the class drove 46% of growth with $1.9 billion sales reflecting 14% of total revenue. These advanced agents are on an impressive upward climb - the GLP-1 agonist market grew 38% YOY in 4Q17 and 32% for the full year, and we note that this is faster growth from a higher base than it had been a year before. It is also faster growth compared to SGLT-2 inhibitors, which as a class grew 24% in 2017 to $3.5 billion. Within the GLP-1 class, Lilly's Trulicity drove the lion's share of growth in 3Q17 (78%), 4Q17 (56%), and 2017 overall (65%). Novo Nordisk's Victoza remains the market leader by value ($3.6 billion represented 55% of pooled sales in 2017, while Trulicity posted $2 billion and captured 31% of pooled sales), but drove a relatively smaller share of growth - 22% in 3Q, 43% in 4Q, and 35% in 2017.

    - **GLP-1 agonists clearly represent an important component of the diabetes industry, and we suspect that sales will continue to soar in 2018.** Novo Nordisk's Ozempic was just recently launched in the US, and semaglutide is widely considered the most potent GLP-1 molecule available today. It will take some time for the company to build reimbursement (though Novo Nordisk is off to a good start with temporary coverage on the Express Scripts formulary), but ultimately, we expect that Ozempic could spur underlying class growth. We've already heard of patients begging for more sample pens because their insurance is not yet covering it. Looking further into the future, oral semaglutide could be another therapeutic option for patients with type 2 diabetes by 2020, and Intarcia's implantable exenatide mini pump (ITCA 650) will also be resubmitted to FDA shortly (following a Complete Response Letter in 3Q17) and could be approved in 2019. We're very excited by this fast-paced innovation in the GLP-1 agonist class, which matches the fast-paced sales growth.

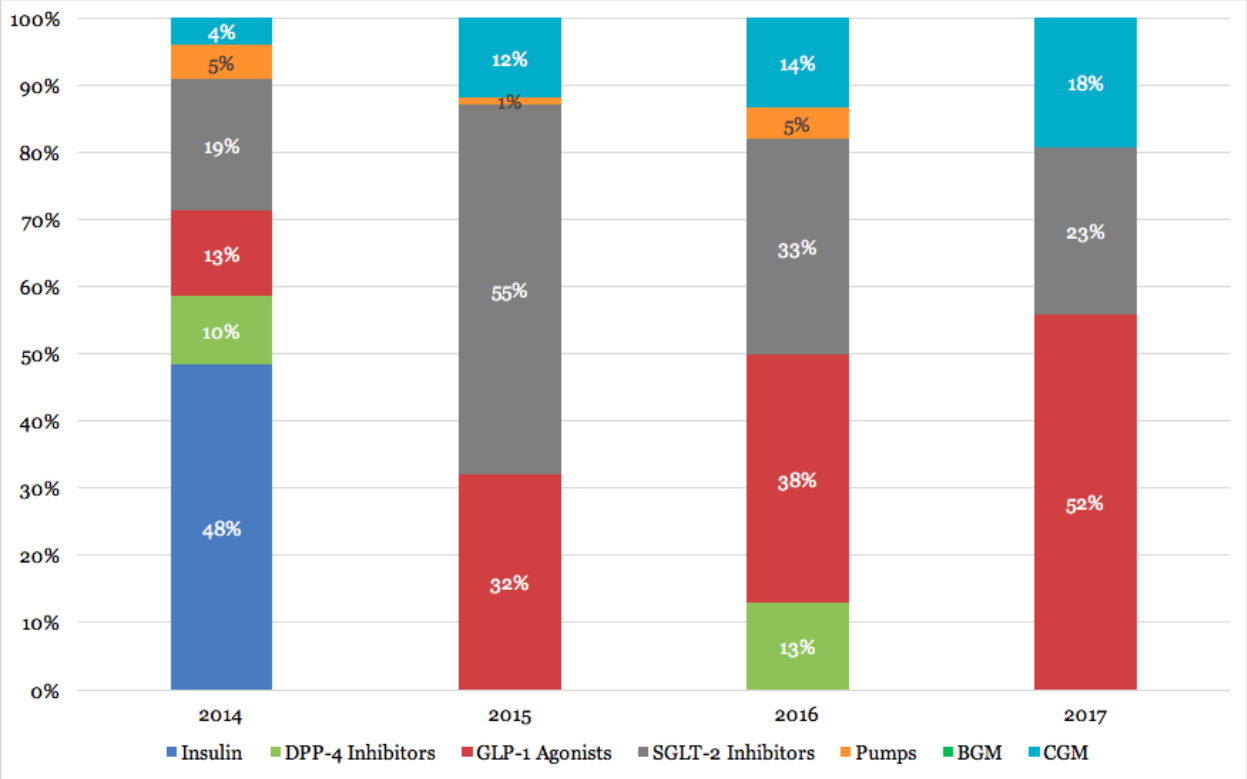
- **SGLT-2 inhibitors drove 23% of industry growth in 2017 ($3.5 billion sales reflected 7% of total revenue), 17% in 4Q17 ($1 billion sales reflecting 8% of total revenue), and 30% in 3Q17 ($935 million sales reflecting 7% of total revenue).** This class of advanced oral agents played a similar role in 1H17, contributing a 16% share of growth in 1Q and a 20% share of growth in 2Q, all while accounting for a smaller proportion of overall sales. While this is strong market growth - there's no doubt about that - we still believe SGLT-2 inhibitor sales could be rising much faster and that they will over time. As you'll see on the graph below, share of growth for this class has fallen substantially from 2015, when it accounted for 55%. There's growing consensus in the field that CV benefit is a class effect of SGLT-2s, since both EMPA-REG OUTCOME and CANVAS were positive. Indeed, we expected a greater burst in SGLT-2 prescriptions/sales after FDA approved a CV indication for Jardiance in late 2016, but this tailwind was met with a headwind in 2017 when FDA added a boxed warning for lower limb amputations to the Invokana label. We discuss these market dynamics in much more detail below, but we do want to emphasize that this class remains a bright spot within the diabetes industry. We see plenty of room for further growth in 2018: Merck/Pfizer just launched Steglatro (ertugliflozin) at a lower list price vs. existing SGLT-2s from Lilly/BI, J&J, and AZ. Moreover, the Invokana business could return to growth with a label update highlighting cardioprotection; an FDA decision on this is expected in 4Q18. This would, in turn, manifest as more dramatic growth for the SGLT-2 inhibitor class as a whole, since the Invokana franchise was the only source of decline in 2017 (-21% YOY to $1.1 billion). Farxiga franchise sales rose 29% YOY to $1.1 billion in 2017, while Jardiance franchise revenue more than doubled YOY to $1.4 billion. We'll be watching quarterly sales closely for the field ...

- **According to our model, CGM drove 18% of overall industry growth in 2017 - worldwide sales of $1.7 billion grew 46% YOY.** This was actually a slight downtick from the record 18%-20% share of growth in 1Q and 2Q, respectively. (That reflects larger growth in other areas of diabetes in 2H17, as the CGM category accelerated in 2H17.) In 2017, we estimate a remarkable ~70% of the CGM field's growth came from outside the US, led by Abbott's FreeStyle Libre (~450,000 users globally). Our model estimates Abbott provided ~50% of the CGM category's

overall 2017 growth ($480 million in sales, doubling YOY), Dexcom provided ~27% ($719 million, +25%), Medtronic provided ~22% (~$502 million, +31%), and Senseonics provided ~1% ($6 million). There is also growing momentum for all four companies: Dexcom's G6 FDA clearance as an iCGM (launch in 2Q18), Medtronic's US Guardian Connect FDA approval (limited launch in May-July), Abbott's 2017 reimbursement victories and run-rate of 50,000 new patient-adds per quarter, and Senseonics's unanimously positive FDA advisory committee. We expect 2018 will be another strong year for CGM, particularly alongside favorable regulatory paradigm shifts (i.e., iCGM pathway), growing consensus around outcomes beyond A1c, and rising views that CGM should be standard of care for intensive insulin users.

    - **Meanwhile, our model suggests that both pumps and BGM declined in 2017.** This was a first for pumps, which have grown every prior year in our model (2005-2016); BGM hasn't grown since 2011.

Diabetes Industry 2017 Share of Growth Graph



Diabetes Therapy

Insulin

Overall Insulin Market Flat at $21 Billion in 2017, $5.4 Billion in 4Q17; US Insulin Sales Falling Consistently (-13% YOY in 4Q17); Bright Spots in Next-Gens and Biosimilars, but Big Three Shifting Focus in Light of Declining Insulin Profitability

- **The injectable insulin market, including basal analogs, rapid-acting analogs, and human insulin products from Novo Nordisk, Sanofi, and Lilly, was flat in 2017 at $21 billion.** In 3Q17, global insulin sales were flat at $5.2 billion, and in 4Q17, the market fell 4% YOY to $5.4 billion (from $5.6 billion in 4Q16). Quarterly insulin sales have hovered around $5 billion

since 2013, while annual sales have hovered around $21 billion, so this 2017 performance matches our general expectations. Basal insulins and mealtime insulins have switched off between modest growth and modest decline to keep this balance at ~$5 billion per quarter and ~$21 billion per year. To this end, the basal insulin class fell 4% YOY in 3Q17 ($2.5 billion), 4Q17 ($2.5 billion), and 2017 overall ($9.9 billion), while rapid-acting insulin revenue grew 7% YOY in 3Q17 ($2 billion), fell 3% YOY in 4Q17 ($2 billion), and rose 4% YOY in 2017 overall ($8 billion). Meanwhile, the market for human insulin experienced single-digit YOY decline in 3Q, 4Q, and 2017, posting $724 million, $791 million, and $3 billion, respectively. See below for a deep dive into each of these insulin categories. Notably, we've separated out basal insulin/GLP-1 fixed-ratio combinations (Sanofi's Soliqua and Novo Nordisk's Xultophy) for this industry analysis, which does take share away from the insulin market - but only ever-so-slightly. Combined Soliqua and Xultophy sales totaled only $142 million in 2017, which pales in comparison to the $21 billion injectable insulin market - for now! Scroll down for our dedicated section on basal/GLP-1.

- **Although insulin hasn't contributed a significant share of growth to the diabetes industry since 2014 (with the exception of an 11% share in 1Q17), this market still comprises the majority of all diabetes drug and device sales.** In 2017, injectable insulin products reflected 43% of total, global industry revenue ($21 billion out of $49 billion). But insulin's value share is getting smaller as the industry grows in single-digit margins (+4% YOY in 2017, +7% YOY in 4Q17) and as pooled insulin sales remain relatively flat year-to-year, quarter-to-quarter. In 4Q17, the insulin market represented 40% of the diabetes industry, down from 41% in 3Q17, 42% in 2Q17, 44% in 1Q17, and so on. Flash back to 2013 and insulin products comprised nearly 50% of the overall industry, according to our records. This is good news for advanced therapy and technology (GLP-1, SGLT-2, CGM) - and we discuss these industry growth drivers above - but it also reveals substantial commercial challenges around insulin. Novo Nordisk CSO Dr. Mads Thomsen told the Wall Street Journal late last year that insulin profitability is at an all-time low; he pointed to US pricing pressure and the (flawed) perception that new insulins offer only marginal rather than disruptive benefit, which lowers a payer's willingness to pay. Next-generation basal insulins (Sanofi's Toujeo and Novo Nordisk's Tresiba) are far, far better than Lantus and Levemir based on our conversations with clinicians and patients. Tresiba's label was just updated by FDA to include DEVOTE data showing a significant 40% risk reduction for severe hypoglycemia vs. Lantus - how is that not a "disruptive" benefit for patients, HCPs, and payers?
    - **We can't ignore these market dynamics affecting insulin profitability, because the Big Three insulin companies are changing their R&D approach in response.** Novo Nordisk explicitly announced a new R&D strategy in late 2016, listing a "higher innovation threshold" (i.e. oral insulin was discontinued from phase 2) and a more deliberate focus on diabetes-adjacent indications like obesity and NASH. Lilly has clearly doubled down on investment in GLP-1 Trulicity and SGLT-2 Jardiance, which is being investigated for chronic heart failure and CKD even outside the context of diabetes. Sanofi will officially expand into obesity and NASH R&D later this year with its GLP-1/glucagon dual agonist (phase 3 studies toward an obesity indication, phase 2 proof-of-concept study for NASH), and the company is also clearly committed to GLP-1 via fixed-ratio combination product Soliqua (insulin glargine/lixisenatide) and phase 3 GLP-1 agonist efpeglenatide. To be sure, we think it goes without saying that Novo Nordisk, Sanofi, and Lilly will remain the Big Three in insulin into the foreseeable future, but they aren't exclusively "insulin companies" anymore. That's not to say these industry players won't continue commercial and clinical development of insulin products, but the insulin market - while sizeable - is no longer the most dynamic piece of the diabetes industry.
- **Looking at insulin sales by geography reveals the impact of US pricing pressure.** Ex-US, the insulin market grew 5% YOY in 3Q17 ($2.5 billion sales), 8% YOY in 4Q17 ($2.6 billion), and 8% YOY in 2017 overall ($10.1 billion vs. $9.3 billion in 2016). US sales negated this growth, falling 5% YOY in 3Q17 ($2.7 billion), 13% YOY in 4Q17 ($2.7 billion), and 3% YOY in 2017 overall ($10.8

billion vs. $11.1 billion). In fact, US insulin sales have dropped consistently since 1Q15, according to our records. Basals and prandials alike face this pricing pressure on the US market, although manufacturers have cited particularly adverse effects within the rapid-acting category, where rebates are high and improving reimbursement is tough. We've heard on several earnings calls that payers view mealtime insulins as interchangeable. Major US formularies often list only one rapid-acting insulin as preferred, excluding the rest, depending on which company agrees to pay the largest rebate. New Lilly CEO Mr. Dave Ricks said at JPM that Humalog and NovoLog are "already on the floor" in terms of pricing, and explained that he's not worried about additional pricing pressure from Sanofi's biosimilar insulin lispro Admelog (approved in December with a US launch planned for 1H18). On Novo Nordisk's 4Q17 earnings call, CEO Mr. Lars Jørgensen suggested that pricing pressure around insulin is a "permanent change" that won't dissipate anytime soon.

- **As of 4Q17, Novo Nordisk held 44% of the global injectable insulin market by value ($2.4 billion) while Sanofi held 32% ($1.7 billion) and Lilly held 24% ($1.3 billion).** This breakdown isn't drastically different from 3Q17 (when Novo Nordisk held 45%, Sanofi held 33%, and Lilly held 22%), or from 1Q17 or 2Q17 (47%, 32%, 21%) for that matter, but there's a pattern here nonetheless. Lilly's share of the insulin market is slowly-but-steadily rising on the strength of biosimilar basal insulin Basaglar. There's more fluctuation in Novo Nordisk's share and in Sanofi's share, because these companies have bright spots in their next-generation basals (Tresiba and Toujeo, respectively) balanced out by their older basal insulins (Levemir and Lantus). Accordingly, only Lilly's insulin business experienced consistent YOY growth in 3Q17 (+16%), 4Q17 (+7%), and 2017 (+10%). Novo Nordisk's insulin business fell 1% YOY in 3Q17, then climbed back up 1% YOY in 4Q17, and grew 5% YOY in 2017 overall, on the strength of Tresiba. Sanofi's insulin business showed consistent YOY decline in 3Q (-10%), 4Q (-13%), and 2017 (-12%), which suggests that Toujeo and Soliqua sales haven't been sufficient to meaningfully buoy the struggling Lantus franchise.
- **Currently, Lilly/BI's Basaglar exists in a one-product class of biosimilar insulins, but a second, third, and fourth biosimilar are imminently arriving.** Merck's Lusduna and Mylan/Biocon's Semglee are also biosimilar formulations of basal insulin glargine (Sanofi's Lantus). Lusduna has been tentatively approved by FDA while Semglee has been filed; full approval/US launch for both products now depends on resolution of Sanofi's patent infringement lawsuits. Semglee was recently approved by the EMA, and European launch is expected to begin in 2H18 (the product is already available in Japan and in select emerging markets). Sanofi's Admelog is the first-to-market biosimilar mealtime insulin; US launch is anticipated in 1H18 (following FDA approval in December), and the product is available in Europe under brand name Insulin lispro Sanofi.
    - **If Basaglar's commercial performance is any indication of how these other biosimilars will fare, this will be a successful class**. Lilly's share of Basaglar revenue (BI's is not reported publically) hit $154 million in 4Q17, tripling YOY and driving 22% of Lilly's diabetes portfolio growth, despite accounting for only 7% of total portfolio sales. Lilly's reported Basaglar revenue reached $432 million in 2017 (its first full year on the US market), quintupling YOY and driving 18% of portfolio growth vs. 6% of total sales. Basaglar is preferred over Lantus on the CVS Health, UnitedHealthcare, and Medicare Part D formularies, which has given the biosimilar a significant edge. On average, biosimilars are listed at a 15%-20% discount to the originator product, so it's not surprising that Basaglar is an attractive option for patients and payers. With Basaglar, diabetes care providers are becoming more familiar with the concept of a biosimilar, more comfortable with equivalent safety/efficacy, which bodes well for the second, third, and fourth products in this class. We suspect that Lusduna and Semglee will lead to further sales decline for Lantus (-21% YOY in 4Q17, -13% YOY in 2017) and Levemir (-18% YOY in 4Q17, -17% YOY in 2017), and we imagine Admelog will introduce more competition for Humalog as well as NovoLog and Apidra, but we're also hopeful that these discounted insulins will reach the many people who aren't currently on insulin therapy but who stand to benefit from it. Expanded choice is a win for patients, and past experience shows that two or more

generics are needed on the market to meaningfully drive down out of pocket costs. For all these reasons, we're excited about Basaglar's impressive performance to-date and we look forward to additional biosimilars coming soon.

- **It's worth noting that the three insulin products doing very well commercially (Basaglar, Tresiba, Toujeo) are innovative in unique ways.** We see biosimilars as innovative for offering equivalent safety and efficacy at a lower price point. Where Basaglar is more affordable, Tresiba and Toujeo offer a flatter PK/PD profile and less day-to-day variability. Tresiba even comes with a flexible dosing claim and has demonstrated significant risk reduction for severe hypoglycemia vs. Lantus - DEVOTE data has been added to Tresiba's US and EU product labels, so marketing of the advanced drug can now highlight its remarkable hypoglycemia benefit. We imagine real-world hypoglycemia rate is also lower for patients on Toujeo vs. Lantus, but this has yet to be shown in a large outcomes trial like DEVOTE. Insulin manufacturers have been candid about declining profitability, and Novo Nordisk CSO Dr. Mads Thomsen emphasized in a WSJ interview that a new insulin today will have to bring meaningful innovation to gain traction on the market. We see Basaglar, Tresiba, and Toujeo each as important advances in diabetes care, though these products too are susceptible to pricing pressure. Going forward, we'll be interested to see how insulin candidates in the pipeline are more seriously scrutinized as the Big Three insulin manufacturers make strategic shifts to focus on other diabetes drug classes and adjacent indications.

Basal Insulin Market Drops ~4% YOY from High Base ($9.9 Billion in 2017, $2.5 Billion in 4Q17); Lantus + Levemir Struggling While Tresiba, Toujeo, Basaglar Soar; Big Win for Tresiba - Hypo Data on Label

- **The basal insulin market fell 4% YOY to $9.9 billion in 2017, declining from a base of $10.3 billion in 2016.** Pooled basal insulin sales dropped 4% YOY and 2% sequentially in 3Q17 ($2.5 billion). In 4Q17, total class revenue dropped 5% YOY but grew 3% sequentially ($2.5 billion). This follows modest declines of 2% YOY and 3% YOY in 1Q17 and 2Q17, respectively. Notably, this financial performance canceled out the modest gains of rapid-acting insulins in 2017 (see below), culminating in an overall insulin market that was flat on the year (see above). While 2017 was sluggish for basal insulins on the whole, we note the very high base for this therapy class - it's still the highest-grossing individual drug or device class in terms of revenue (DPP-4s came in second with $9.7 billion for the year, and mealtime insulins were third with $8 billion), and basals still make up 47% of the insulin market (with a smaller share going to bolus insulins and human insulins). The present analysis covers basal analogs old and new, including Sanofi's Lantus (insulin glargine U100), Novo Nordisk's Levemir (insulin detemir), Sanofi's Toujeo (insulin glargine U300), Novo Nordisk's Tresiba (insulin degludec), and Lilly/BI's Basaglar (biosimilar insulin glargine); only Lilly's share of Basaglar sales (and not BI's) is reported publically, so our value for Basaglar underestimates total global revenue.
    - **In any case, the decline in basal insulin sales throughout 2017 was driven by Lantus and Levemir.** Sanofi management anticipated major headwinds for the Lantus franchise, since the product was excluded in favor of Basaglar on the CVS Health and UnitedHealthcare formularies in 2017 (this has carried over into 2018, and now Lantus is also on a higher tier with lower reimbursement vs. Basaglar on the Medicare Part D formulary). In line with this expectation (Sanofi's financial guidance projects 6%-8% annual loss in the diabetes business over 2015-2018), worldwide Lantus sales fell 20% YOY in 3Q17, 27% YOY in 4Q17, and 19% YOY in 2017 to $7.2 billion, which is the lowest annual revenue recorded for the franchise since 2011 ($6.3 billion in 2011, $7.4 billion in 2012, $8.7 billion in 2013, $9.7 billion in 2014, $8.4 billion in 2015, and $8.1 billion in 2016). Levemir also had a challenging fiscal year, with sales dropping 27% YOY in 3Q, 18% YOY in 4Q, and 17% YOY in 2017 to $2.2 billion. That Levemir fell by a similar margin from a much lower base vs. Lantus is certainly a negative sign, and it's all the more reason that

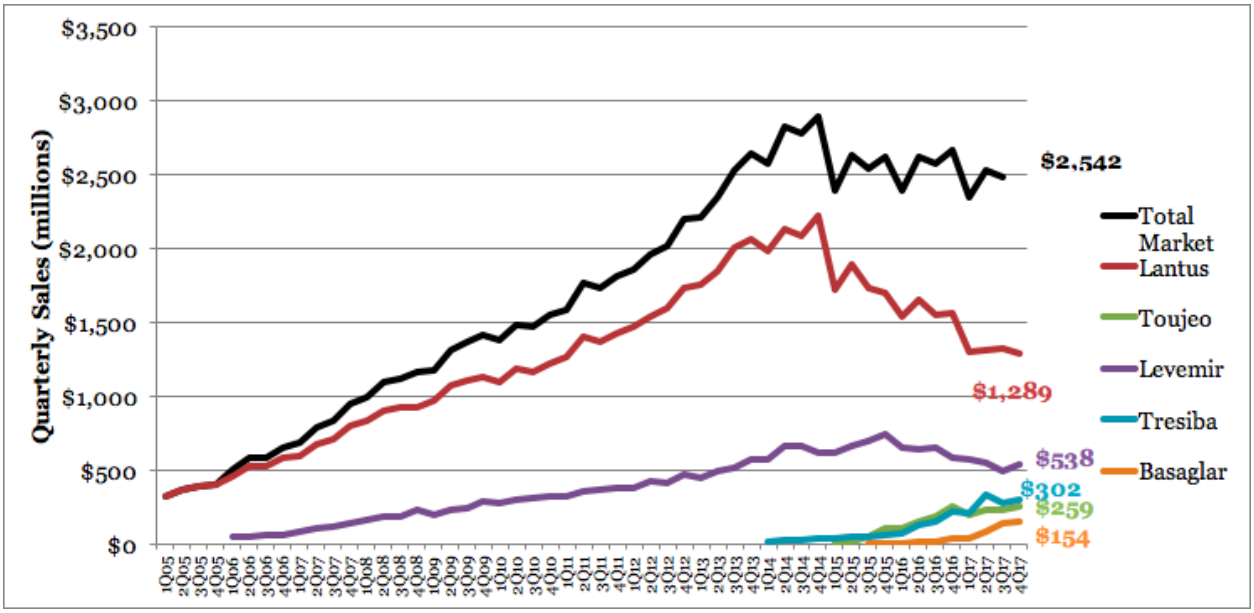
Novo Nordisk and Sanofi are focusing on their next-generation basals to stimulate portfolio growth.

- **Indeed, pooled sales of Tresiba and Toujeo rose 57% YOY to $2.1 billion in 2017.** This was from a base of $1.3 billion in 2016, and the next-gen class also grew 18% YOY and 10% sequentially in 4Q17 to $561 million (from $475 million in 4Q16 and $510 million in 3Q17). While these YOY jumps are impressive, this was an easy sequential comparison in 4Q since pooled Tresiba and Toujeo revenue fell 10% sequentially in 3Q (+48% YOY to $510 million). Nevertheless, both these products continue to shine, contributing to portfolio growth for each company, buoying the basal insulin class in light of falling Lantus/Levemir sales, and improving patient outcomes in the real world. Although Toujeo took a disappointing dip in 4Q17 revenue (-4% YOY to $259 million), both advanced basals posted impressive sales in 2017 overall (Tresiba +80% YOY to $1.1 billion, Toujeo +26% YOY to $926 million). As of 4Q17, these two next-gen products captured 22% of the $2.5 billion basal insulin market, up from 18% in 4Q16 and 21% in 3Q17 - this is remarkable, in our view, and we imagine this value share will only climb now that Tresiba has DEVOTE data underlining hypoglycemia benefit on its label.
- **Moreover, Novo Nordisk and Sanofi have stated that they don't expect the Levemir and Lantus businesses to really recover, and neither do we considering that much better products are now available and are generally well-reimbursed (though there's certainly room for improvement).** Tresiba captured 54% of next-gen pooled sales in 4Q17, and Toujeo held the remaining 46%. Tresiba's market share by value has increased steadily (47% in 4Q16), and it also outpaced Toujeo in market share by volume in 2017, holding 11% of total basal insulin prescriptions (TRx) in the US as of January 2018 compared to Toujeo's 8%. Novo Nordisk met its goal of surpassing 10% TRx with Tresiba by year-end. Of note, head-to-head studies of Tresiba vs. Toujeo are now underway and are already generating a fair amount of buzz in the diabetes community. The Sanofi-sponsored BRIGHT study wrapped up in August 2017: Preliminary results were presented at ATTD, and the company also issued a topline release in December, but we're eagerly awaiting ADA in June for the full results including hypoglycemia findings. A Novo Nordisk-sponsored head-to-head trial is expected to complete in December 2018 per ClinicalTrials.gov, and the company has promised data in 4Q18. Of the numerous clinical benefits that come with these advanced drugs, lower hypoglycemia risk tops the list in our opinion, and we imagine there will only be more discussion of hypoglycemia in the context of basal insulin selection following Tresiba's recent label update (groundbreaking for the regulatory world!). Of course, we'd also love to see more on time-in-range, if the companies can get CGM into their studies.
- **Basaglar had a positive year as well, competing directly with Lantus (and also with Levemir) following US launch in mid-December 2016.** Global revenue quintupled in 2017 to $423 million, including $310 million from the US market, although this was from a low base of $86 million in 2016. In 4Q17, revenue more than tripled YOY to $154 million (vs. $40 million in 4Q16), including $114 million in US sales. Basaglar seems to have benefited immensely from its preferred status on the CVS Health and UnitedHealthcare formularies; this was implemented in 2017 and remains in effect for 2018, which leads us to believe that Lilly/BI's biosimilar will only continue to "steal share" from Lantus and Levemir in quarters to come. That said, there are so many people with diabetes in the US and globally who could benefit from basal insulin therapy even though they aren't currently taking it, and we're keeping our fingers crossed that Basaglar and other upcoming biosimilars (listed at an approximate 15%-20% discount) will reach some of these patients in-need.

- **Lantus held 51% of the basal insulin market by value in 4Q17 with $1.3 billion sales - this value share is dropping steadily (53% in 3Q17, 59% in 4Q16).** Levemir held 21%

market share by value with $538 million sales in 4Q17, while Tresiba held 12% with $302 million and Toujeo held 10% with $259 million. Basaglar held 6% with $154 million revenue - this value share is notably climbing (just under 6% in 3Q17, <2% in 4Q16). By company, Novo Nordisk captured 33% of pooled basal insulins sales in 4Q with Levemir and Tresiba combined; Sanofi's insulin glargine franchise remains the frontrunner with 61% of the entire market, and Lilly/BI hold the last 6% with Basaglar. One year ago, in 4Q16, Novo Nordisk captured 30% of the basal insulin market vs. Sanofi's 69% and Lilly/BI's <2% (Basaglar had literally *just* launched in the US), which goes to show that Lantus' fall is outpacing Toujeo's growth (hence, Sanofi lost ~8% value share in 2017). By volume, Lantus accounted for 45% of total basal insulin prescriptions in the US (TRx) as of January 2016, according to Novo Nordisk's 4Q17 earnings presentation. Levemir held 23% US TRx in January 2018, followed by Tresiba with 11%, Toujeo with 8%, and Basaglar with 6%. Novo Nordisk's total share of the basal insulin market by volume is ~34%, Sanofi's is ~52%, and Lilly/BI's is ~6%; we suspect the remaining 8% goes to non-branded/human basal insulins. Lantus' TRx fell 4% from 49% as of October 2017, and in the same three months, Tresiba's TRx climbed 2% from 9%, while Basaglar's TRx climbed 2% from 4%. This suggests that more basal insulin prescriptions (whether new patient starts or switches) are going to the next-generation product and to the biosimilar over first-generation Lantus and Levemir.

Basal Insulin Market (1Q05-4Q17)



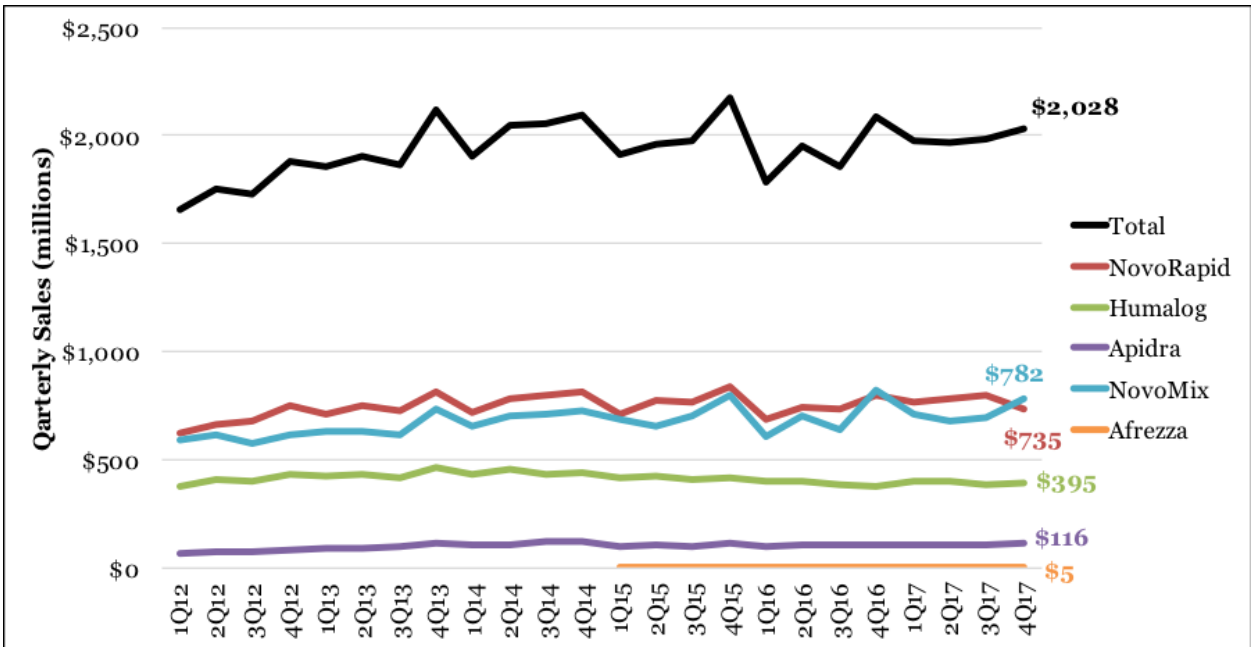
Rapid-Acting Insulin Market Grows 4% YOY to $8 Billion in 2017, Led by Humalog and NovoLog; Whole Class Sales Continue to Fluctuate

- **On pace with 1H17, the rapid-acting insulin class grew 4% YOY in 2017 to $8 billion. We were actually surprised to see growth here given growth in other areas like GLP-1 and SGLT-2 (which also address postprandial excursions.)** This market (including Novo Nordisk's NovoMix) has hovered around $8 billion annually for several years: $7.7 billion in 2016, $8 billion in 2015, and $8 billion in 2014. Pooled mealtime insulin sales rose 7% YOY in 3Q17 to $2 billion (-1% sequentially), and then fell 3% YOY in 4Q17 to $2 billion (+2% sequentially). Whole class revenue continues to fluctuate - for context, the market declined 5% YOY in 2016 and 2% YOY in 4Q16. On the one hand, 2017 featured an unremarkable financial performance from rapid-acting insulin analogs (as far as we can tell - profitability is obviously not reported by all the players and real prices are unknown). However, considering the steep challenges in this market, it's worth calling out even modest growth. Pricing pressure is especially tough around mealtime insulins, because as we understand it, payers view these products as largely interchangeable and thus restrict

formulary access and negotiate higher rebates from the manufacturer. As just one glaring example, we came across this stirring blog post written by a patient under the UnitedHealthcare umbrella who couldn't get an Afrezza prescription reimbursed despite profound benefits of inhalable insulin to his personal diabetes management. Beyond pricing pressure, rapid-acting analogs also face intense competition from GLP-1 agonists and SGLT-2 inhibitors, advanced diabetes drug classes that address postprandial glucose excursions without excess hypoglycemia risk. This class accounted for 38% of the overall injectable insulin market in 4Q17 and in 2017, which is on par with previous quarters (38% in 3Q17, 37% in 2Q17, 39% in 1Q17, 38% in 4Q16, 36% in 3Q16, and so on); we attribute these slight differences quarter-to-quarter to fluctuating sales in all insulin categories, including basal, bolus, and human.

- **Lilly's Humalog (insulin lispro) and Novo Nordisk's NovoLog (insulin aspart) dominate the rapid-acting insulin class in terms of revenue, capturing 39% ($782 million) and 36% ($735 million) of the $2 billion market in 4Q17.** Humalog and NovoLog have switched back-and-forth for the lead: In 3Q17, Humalog held 35% of this market by value while NovoLog held 40%, and in 4Q16, Humalog was on top with 39% while NovoLog was in a close second with 38%. Also included in our rapid-acting insulin analysis are NovoMix (19% value share in 4Q17 with $395 million sales) and Sanofi's insulin glulisine product Apidra (6% value share with $116 million). Market share by value for NovoMix and Apidra has stayed relatively constant at ~20% and ~5% since 2012.
- **Equally interesting is what's not included in the present analysis: Novo Nordisk's next-generation mealtime insulin Fiasp (faster-acting insulin aspart) and MannKind's inhalable Afrezza.** Novo Nordisk has yet to break out Fiasp sales, but the product was wrapped into the "new-generation insulin" portfolio for the sake of financial reporting as of 3Q17. Fiasp was launched only recently to US pharmacies (early February), so we wouldn't expect meaningful revenue in 2H17, although we estimate OUS sales at <$20 million to-date (calculated by subtracting reported Tresiba, Xultophy, and Ryzodeg sales from the total revenue listed next to "new-generation insulins"). There's been some disagreement among diabetes thought leaders on how much value Fiasp adds for patients (UW's Dr. Irl Hirsch was less than impressed at Endo Fellows last month), but we maintain that any increase in onset/offset speed is an important advance in diabetes care. Mealtime insulin is simply not good enough - it's a difficult drug to prescribe and to dose - so we'll take any improvement over none at all. MannKind's Afrezza showed a strong financial performance in 4Q17 ($4.5 million sales, more than tripling YOY and more than doubling QOQ), but this followed a very sluggish 1Q17, 2Q17, and 3Q17, and product revenue still reflects a tiny portion of the rapid-acting insulin market as a whole (<1%). There's hope for Afrezza in 2018 and beyond now that the FDA has approved an ultra-rapid-acting label claim (displaying significantly faster onset/offset vs. Lilly's Humalog), and we'll be watching this rollout with keen interest.

Rapid-Acting Insulin Market (1Q12-4Q17)



Human Insulin Sales Fall 5% YOY to $3 Billion in 2017; Novo Nordisk Holds 50% of Market by Value, Followed by Lilly (46%), Sanofi (4%)

- **Human insulin sales from Novo Nordisk, Sanofi, and Lilly declined 5% YOY to $3 billion in 2017, reflecting 14% of the overall injectable insulin market.** Pooled sales also dropped 6% YOY in 3Q17 to $724 million (representing 14% of the entire market) and fell 2% YOY in 4Q17 to $791 million (15% of the entire market). This class seems to be following the same pattern as basal insulin and mealtime insulin analogs - that is, a trend of fluctuating sales, with single-digit growth or decline every quarter. For context, pooled revenue from human insulins was flat in 2Q17, down 10% YOY in 1Q17, flat in 4Q16 and 3Q16, up 1% in 2Q16, etc. Interestingly, Dr. Irl Hirsch has implied that prescription volume for this class may rise noticeably in 2018 and beyond, as many more patients go on human insulin. To be sure, high price keeps branded insulin products out of reach for many; the population of diabetes patients requiring insulin therapy is also increasing in number (according to ADA's latest cost analysis, the US spent $15 billion on insulin in 2017). The majority of human insulin sales in 4Q17 went to Novo Nordisk - $397 million (-9% YOY), or 50% of the $791 million total. Lilly captured 46% of the market by value with Humulin revenue of $363 million in 4Q17 (+2% YOY). Sanofi held the remaining 4% of market share with Insuman sales of $31 million (-16% YOY).

GLP-1 Agonists

GLP-1 Agonist Sales Rise 32% YOY for $6.5 Billion in 2017, Driving 52% (!) of Industry Growth; Trulicity Drives Class Growth; Victoza Benefits from New CV Indication

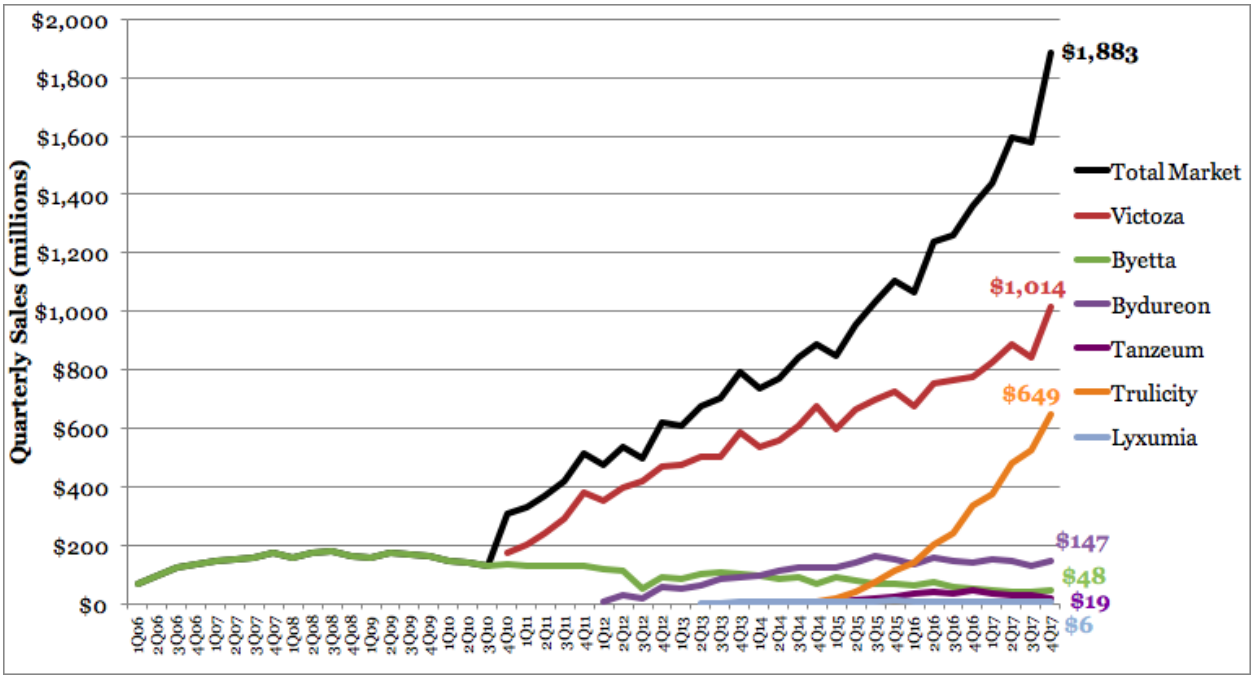
- **The GLP-1 agonist class continued to climb skyward in the second half of 2017 - pooled sales increased 32% on the year, reaching an all-time high of $6.5 billion vs. $4.9 billion in 2016.** GLP-1 revenue rose 25% YOY in 3Q17 (-1% sequentially, an inconsequential dip all things considered) to $1.6 billion. Market growth was outstanding in 4Q17, +38% YOY and +19% sequentially to $1.9 billion. In fact, this 38% YOY jump in 4Q was the largest the class has seen since 3Q13, driven by a sharp upward trajectory for both Novo Nordisk's Victoza (liraglutide) and Lilly's Trulicity (dulaglutide). This builds on solid GLP-1 agonist growth of 35% YOY in 1Q17, 29% YOY in 2Q17, and 25% YOY in 2016. We've said it before and we'll say it again: This class is growing rapidly

from a high base, which is exciting to see for products that are so effective in glucose-lowering, weight loss, and possible cardioprotection (more on this below). GLP-1 agonists were the no. 1 industry growth driver in 2H17, reprising their role from 1H17. By our calculations, GLP-1s contributed a 38% share of growth in 3Q17 while reflecting only 13% of total industry revenue (this encompasses drugs and devices). In 4Q17, GLP-1s drove 46% of industry growth and reflected 14% of total revenue. And in 2017 overall, the class drove a whopping 52% of growth and reflected 13% of revenue, meaning GLP-1 agonists have been vital in propelling the industry forward. For additional context, note that the GLP-1 class has now surpassed the rapid-acting insulin market in total sales ($1.9 billion vs. $1.6 billion in 4Q17); indeed, an important benefit of GLP-1s is how they address postprandial excursions without excess risk of hypoglycemia, and a bolus insulin is certainly more complicated for providers to prescribe and for patients to take. We're encouraged by the commercial performance of GLP-1 agonists in 2017, and we're glad to see increased adoption of these superior agents. What's more, there's still substantial head room for growth in 2018 and beyond. With $6.5 billion recorded in all of 2017, the GLP-1 market represents a mere fraction (~31%) of the injectable insulin market ($21 billion) and still lags behind the basal insulin market ($9.9 billion). To this end, Lilly management has mentioned that the number of GLP-1 agonist prescriptions is equivalent to only ~30% of basal insulin prescriptions worldwide (we wonder if basal/GLP-1 combos could ease the transition onto GLP-1 therapy, although uptake of these fixed-ratio combinations has been extremely sluggish to-date, which continues to be very disappointing to us given their efficacy). A Diabetes Care analysis published last year found that only 7% of second-line diabetes prescriptions in the US are for GLP-1 agonists, which is disappointingly (read: absurdly) low in our view. We consider 2017 a very positive year for GLP-1 agonists nonetheless, and we're optimistic about upcoming innovation (detailed below) that could spur further class growth along with recently FDA-approved Ozempic.

- **In terms of market share by value, Victoza maintained its lead with 54% in both 3Q17 and 4Q17 (posting $884 million and then $1 billion in quarterly sales). Trulicity followed with 34% market share by value in both quarters ($528 million and $649 million, respectively).** That said, Trulicity was the primary growth driver for the class in 2H17. In 3Q, Trulicity contributed an impressive 78% share of growth vs. Victoza's 22%, even though Trulicity sales only reflected 34% of whole class revenue vs. Victoza's 54%. In 4Q, Trulicity drove 56% of market growth while Victoza drove 43%. In 2017 overall, Trulicity drove 65% of growth while capturing 32% of pooled sales, and Victoza drove 35% of growth while claiming 55% of pooled sales. In line with this pattern, Trulicity revenue more than doubled YOY in both 3Q and 4Q17; Victoza revenue rose 5% YOY and 17% YOY, respectively, from a higher base. The gap between these two market-leading GLP-1s is narrowing (i.e. Trulicity is catching up) - in the first half of 2017, Victoza held 56%-57% of the market by value while Trulicity held 26%-30%. Volume trends reveal the same: Victoza captured 46% of total GLP-1 agonist prescriptions (TRx) written in the US as of May 2017, which dropped slightly to 44% by November 2017. Trulicity's US TRx was 36% in May 2017 and 37% in November 2017. We're looking forward to 1Q18 numbers in just a few weeks.
    - **The other GLP-1 agonists available today represent a smaller share of the overall market.** This includes AZ's Bydureon (exenatide once-weekly) and Byetta (exenatide twice-daily), GSK's Tanzeum (albiglutide once-weekly), and Sanofi's Adlyxin (lixisenatide once-daily). Bydureon sales fell 12% YOY in 3Q17 to $128 million, reflecting 8% of pooled GLP-1 revenue, and grew 4% YOY in 4Q17 to $147 million, when they again reflected 8% of pooled revenue. Byetta sales dropped 36% YOY in 3Q17 to $39 million (2% of the market by value), and fell 13% YOY in 4Q17 to $48 million (3% of the market by value). GSK has announced plans to withdraw support from Tanzeum, but the company continued to report these sales in 2H17, which came in at $29 million for 3Q17 (-24% YOY, 2% of the market by value) and $19 million for 4Q17 (-58% YOY, 1% of the market by value). Sanofi's Adlyxin remains at <1% market share; product sales declined 22% YOY in 4Q17 to $6 million. It's worth noting that this breakdown of market share by value has been pretty steady, which suggests strong underlying class growth (i.e. despite significant

competition within the GLP-1 agonist class, all products are benefiting from underlying growth drivers like greater PCP adoption). We expect Bydureon sales to improve with recently approved BCise.

GLP-1 Agonist Sales (1Q06-4Q17)



- **GLP-1 agonists are handily outpacing SGLT-2 inhibitors, growing faster from a higher base.** Pooled SGLT-2 sales rose 24% YOY to $3.5 billion in 2017, compared to a 32% YOY jump to $6.5 billion for GLP-1s. This steeper slope is particularly notable given that SGLT-2s are "newer," strictly speaking, available since 2013-2014 vs. 2006 for Byetta, 2010 for Victoza. As such, we might expect the SGLT-2 market to be growing more rapidly, as these products are earlier in their lifecycle and should be growing faster as a class even if just due to the lower base. The difference in speed of growth likely reflects safety concerns surrounding SGLT-2 inhibitors, namely amputations and bone fractures (and possibly DKA), but more importantly, we think it highlights the ongoing innovation in GLP-1 agonist therapy. Since 2010, once-weekly GLP-1s have become available, and patients now have access to easy-to-use autoinjectors (the IDEO-designed Trulicity pen, Bydureon BCise). CVOTs have revealed CV benefit associated with molecules like liraglutide and semaglutide, and many thought leaders are positioning cardioprotection as a GLP-1 class effect (though this is still the source of some debate).
- **Several events over the past year illustrated just how critical CV outcomes are in the GLP-1 agonist class: Bydureon sales dropped after neutral EXSCEL results read out at EASD (-12% YOY in 3Q17), while Victoza experienced a boost in 4Q17 (+17% YOY) following 3Q17 approval of a CV indication from FDA.** While many thought leaders have characterized EXSCEL results as positive and supportive of a cardioprotective class effect (Drs. Ralph DeFronzo, Rury Holman, Francesco Giorgino, and others), a hazard ratio for three-point MACE that just misses statistical significance for superiority (HR=0.91, 95% CI: 0.83-1.00, p=0.06 for superiority) won't be enough for FDA to grant Bydureon a CV indication. As far as we're aware, AZ has not yet filed anything with FDA requesting any sort of EXSCEL-based label update. This is unfortunate since EXSCEL's technically neutral results have been widely attributed to a pragmatic study design, including a larger primary prevention cohort, the use of single-dose Bydureon reconstitution kits, no run-in period to exclude patients with poor adherence, a wide range of concomitant medications allowed, etc. There are distinct advantages to a pragmatic trial like this in terms of what we can learn that's directly applicable to real-world patients. But the sales numbers

don't lie. During Novo Nordisk's Capital Markets Day last November, management pointed to an inflection point in Victoza sales following re-launch with the new CV indication. There's a clear downside for AZ in not being able to claim CV benefit on the label, not being able to promote CV efficacy in marketing Bydureon to patients, HCPs, and payers. Moreover, patients benefit when sales reps are in the field discussing diabetes and CV risk, and we'd love to see more industry players be able to participate in the awareness campaign. Ultimately, as the diabetes treatment paradigm shifts more and more toward CV risk reduction, we believe demonstrating CV efficacy is only going to become more important, for GLP-1 agonists and all diabetes drugs. We continue to wish that an all-drug CVOT were possible - although this continues to be characterized as "too expensive" it is so inexpensive when the costs in the field are considered (preventable CVD, for example).

    - **REWIND, Lilly's CVOT for Trulicity, is expected to complete in July 2018. Topline results are anticipated by year-end.** This trial will have major implications in the debate over (i) whether cardioprotection is a class effect for GLP-1s and (ii) whether GLP-1s offer cardioprotection in a primary prevention population. So far, only Novo Nordisk's liraglutide and semaglutide have demonstrated CV superiority, and only liraglutide (Victoza) has a CV indication on its label. SUSTAIN 6 for semaglutide was a relatively small, relatively short trial, so Novo Nordisk will launch the SOUL CVOT (n=13,000) later this year to hopefully produce evidence for cardioprotection that is more compelling in a Supplementary New Drug Application.

- **What's next for the GLP-1 agonist class? The recent US launch of Novo Nordisk's Ozempic (once-weekly semaglutide) could markedly change class-wide dynamics, though we see great potential for Ozempic to stimulate whole class growth.** Time will tell how the field approaches Ozempic - we believe it will be very positive overall. Will HCPs consider it cardioprotective without an official indication? Will patients prefer it to Victoza for the lower injection burden? Will payers appreciate the potential cost-savings given semaglutide's incredible potency as a glucose-lowering, weight-lowering molecule? While Victoza and Trulicity both garnered impressive commercial success before and without a CV indication, CV benefits are becoming ever-more important for diabetes drugs. That said, semaglutide offers an unprecedented level of efficacy cardioprotection aside; Ozempic even showed superiority to Trulicity on A1c-lowering and weight loss in the recently-published SUSTAIN 7 trial. Lilly management has maintained that their patient-friendly autoinjector will allow Trulicity to compete with Ozempic. The way we see it, adding Ozempic as another GLP-1 agonist option opens the door for better treatment personalization. We expect Ozempic to drive overall class growth more than anything else.

    - **The GLP-1 excitement extends to the pipeline, with Novo Nordisk's oral semaglutide nearing the end of phase 3 trials and Intarcia gearing up for resubmission of implantable exenatide mini pump ITCA 650, following an FDA Complete Response Letter in September.** All 10 studies in the PIONEER program for oral semaglutide will read out in 2018 (PIONEER 1 topline results are already out and seem quite positive). Novo Nordisk is targeting 2019 for an NDA filing for the first-ever oral GLP-1 agonist. This will bring very meaningful innovation to the class and to treatment algorithms - the efficacy of a GLP-1 agonist in a pill would be hugely disruptive and a big win for patients, though we have picked up on some concerns over strict fasting requirements around each dose (i.e. oral semaglutide has to be taken on an empty stomach, you have to wait ~30 minutes to eat afterward). Novo Nordisk expects oral sema to compete with other oral agents (SGLT-2s, DPP-4s) rather than injectable GLP-1s. In our dream world, Novo Nordisk would develop a fixed-dose combo with oral semaglutide + an SGLT-2 inhibitor, though the company doesn't have an SGLT-2 in its current portfolio and we're not sure the carrier necessary for the oral semaglutide formulation would allow this. Also in the late-stage pipeline, Intarcia's ITCA 650 received a CRL in September 2017, but our understanding is that the company remains fully dedicated and is working to resubmit as swiftly as possible. Resolving FDA's concerns won't require any new pivotal trials.

- **Sanofi also initiated a phase 3 trial for once-weekly efpeglenatide in 4Q17.** This study isn't scheduled to complete until February 2020, but phase 2 showed promising efficacy - indeed, we're curious why it look so long to initiate phase 3. Admittedly, we were excited when this trial was announced because prior studies had indicated potential for once-monthly dosing, but Sanofi management has stated that they won't pursue once-monthly dosing due to an anticipated drop in efficacy. It's a bit difficult to imagine huge commercial prospects for efpeglenatide, given that it would likely come to market around the time other GLP-1s are starting to go generic. We're curious if Sanofi has plans to pursue a fixed-ratio combination with basal insulin. Indeed, our sense is that standalone lixisenatide (Adlyxin) was never a top commercial priority for the company, but rather was a stepping stone to Soliqua (insulin glargine/lixisenatide). A once-weekly agent in this fixed-ratio class (Soliqua and Novo Nordisk's Xultophy both require daily injections) could be transformative, but we can only speculate for now. More on basal/GLP-1 combos below.

Basal Insulin/GLP-1 Fixed-Ratio Combinations

Sluggish Performance from Basal/GLP-1 Combos: $142 Million in Full Year Sales; 45% Sequential Growth to $54 Million in 4Q17; Xultophy Holds Majority Share (~80%) of Market by Value

- **The two basal insulin/GLP-1 agonist fixed-ratio combinations on the market - Novo Nordisk's Xultophy (insulin degludec/liraglutide) and Sanofi's Soliqua (insulin glargine/lixisenatide) - together posted $142 million in 2017.** This was the first full year with both products available: After FDA approved LixiLan and IDegLira on the same day in late November 2016, Soliqua was launched to US pharmacies in early January 2017, and while Xultophy was already on the market in Europe, it wasn't available for US patients until May 2017. For two therapies so early in their launch cycle, $142 million in annual revenue is extremely underwhelming. Pooled sales increased by a mere 12% sequentially to $37 million in 3Q17 (from a base of $33 million in 2Q17), and grew 45% sequentially to $54 million in 4Q17. This is the first time we've included basal/GLP-1 combos in our industry roundup, and the class drove ~5% of industry growth in 3Q17, 4Q17, and 2017 overall (while reflecting <1% of industry-wide revenue), only because it didn't exist on the market in 2016. Over the course of the year, we noticed that commercial enthusiasm for fixed-ratio combination therapy was lagging behind clinical enthusiasm, in that thought leaders have been very generous in their praise for these agents. Dr. John Buse has gone so far as to call Xultophy "the most effective anti-hyperglycemic agent on the planet." Both drugs in this class offer superior A1c-lowering efficacy vs. either monotherapy, and Xultophy in particular has demonstrated a significant weight loss benefit. A meta-analysis across the DUAL program found that ~80% of patients randomized to Xultophy achieved A1c <7% without weight gain or severe hypoglycemia; in contrast, only ~37% of patients on standalone liraglutide (Victoza) and only ~15% on insulin glargine alone (Sanofi's Lantus) achieved this composite endpoint. Taking basal insulin and GLP-1 simultaneously allows for lower doses of each molecule and thus mitigates side-effects (less hypoglycemia, fewer GI issues). Fixed-ratio combination treatment can also improve adherence, thereby increasing treatment satisfaction and leading to better patient outcomes - as one example, PROs from DUAL VII favored Xultophy over basal-bolus in terms of willingness to continue treatment after 26 weeks, treatment burden, and diabetes management. These are all meaningful benefits for patient quality of life and for the ultimate success of diabetes care, and one of our greatest disappointments of 2017 was that Xultophy and Soliqua didn't reach more patients. Reimbursement remains a challenge, and HCPs in the US seem reluctant to prescribe fixed-ratio combinations due to concerns over parsing out side-effects. Again, we emphasize that these drugs offer a milder side-effect profile vs. a GLP-1 agonist or basal insulin alone, and they show impressive treatment satisfaction scores in clinical trials (we have strong reason to believe this will carry over into the real world as well).

- **Individual product performance was similarly disappointing in 2017.** Xultophy sales were flat sequentially in 3Q17 ($28 million - exactly matching 2Q17 revenue). The franchise fared somewhat better in 4Q17, with revenue rising 51% sequentially to $43 million and bringing annual sales to $112 million. Soliqua sales grew 60% sequentially to $9 million in 3Q17, from the very low base of $6 million in 2Q17; revenue in 4Q17 grew 13% sequentially to $11 million, bringing the annual sum to $30 million. Based on these reported sales, Xultophy held ~80% of the market by value at the end of the year. In fact, Novo Nordisk captured the majority of class-wide revenue throughout the year (79% in 1Q17, 85% in 2Q17, and 76% in 3Q17). It'll be interesting to see if this changes as Sanofi invests more commercially in the Soliqua business; Novo Nordisk has shared an explicit strategy to de-prioritize Xultophy until the diabetes community is more familiar with standalone insulin degludec (Tresiba) and standalone liraglutide (Victoza). For Sanofi's part, the company is sponsoring peer-to-peer medical education to familiarize HCPs with the concept of a fixed-ratio combination (which is actually easier to prescribe and comes with milder side-effects, contrary to common misconceptions). Sanofi management is also working to improve reimbursement. These efforts could help grow the class, and we sincerely hope that combined Xultophy + Soliqua sales are more impressive in 2018 vs. 2017; we'll get our first glimpse at this once 1Q18 earnings season begins in a couple weeks. We can't help but wonder how prescription volume and sales for this class might take off with both Novo Nordisk and Sanofi investing strategically, using their extensive experience marketing diabetes drugs, and we hope to see more action from Novo Nordisk in 2018. After all, if Xultophy really is "the most effective anti-hyperglycemic agent on the planet," it's a travesty that the product isn't being prescribed at much, much higher volumes.

SGLT-2 Inhibitors

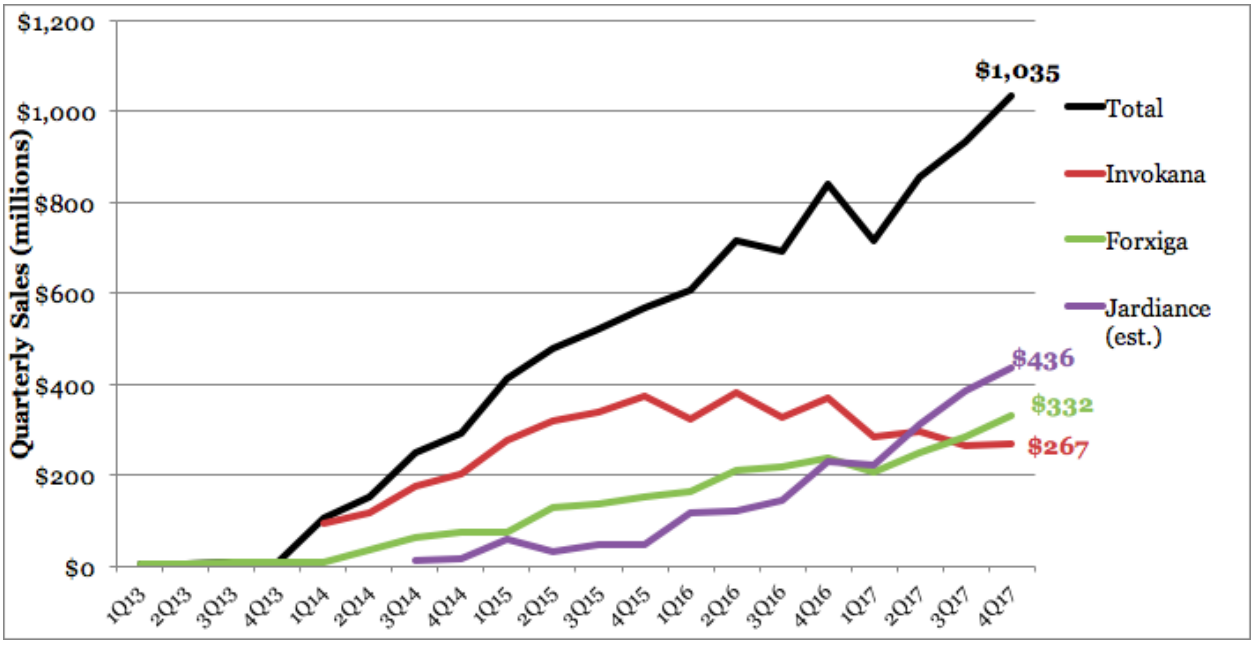
SGLT-2 Inhibitor Market Grows 24% YOY to $3.5 Billion in 2017; Hits Blockbuster Status with $1 Billion Quarterly Revenue in 4Q17; Jardiance "Stealing Share" from Invokana Amidst Rising Concern Over Amputations

- **SGLT-2 inhibitors as a class showed encouraging growth in 2H17, with pooled revenue rising 35% YOY to $935 million in 3Q17 and then 23% YOY to just over $1 billion in 4Q17 (the first-ever blockbuster quarter for SGLT-2s). In 2017 overall, the SGLT-2 market climbed 24% YOY to $3.5 billion, from $2.9 billion in 2016.** This was a strong financial performance following lower growth in 1H17 (+18% YOY in 1Q, +20% YOY in 2Q), but 2H17 growth is still slower than we'd expect for a class with two positive CVOTs and one product with a CV indication on its label (Lilly/BI's Jardiance received this from FDA in December 2016). The sales trajectory for SGLT-2s noticeably decelerated in 2017 vs. 2016, when quarterly YOY growth was +47% in 1Q16, +49% in 2Q16, +33% in 3Q16, and +48% in 4Q16, culminating in 44% growth on the year. Moreover, GLP-1 agonists (which have been on the market for longer) are growing faster from a higher base than SGLT-2 inhibitors, which is another sign that pooled SGLT-2 sales could be on a steeper climb. SGLT-2s are oral where GLP-1s are injectable, meaning they're a more convenient option for patients and are probably simpler to prescribe.
- **There's also increasing buzz in the diabetes field surrounding a cardioprotective class effect for SGLT-2 inhibitors** (while a CV class effect remains controversial for GLP-1s), and cardiologists are currently more keen on SGLT-2s because that field is less familiar with injectable drugs. Given all this, we might expect SGLT-2s to be doing at least as well commercially as GLP-1s. But the class has been held back by concern over lower limb amputations: In May 2017, FDA added a boxed warning to the Invokana label (J&J's canagliflozin), and CANVAS found nearly two-fold risk for a lower-extremity amputation with canagliflozin vs. placebo. In line with this, 2017 was a tough year for the Invokana business, which fell 19% YOY in 3Q17 to $265 million and 28% YOY in 4Q17 to $267 million (-21% on the year to $1.1 billion). J&J management has attributed the decline to higher patient discounts (and indeed, diaTribe found J&J's patient assistance program to be one of the best

for a diabetes pharma company), but we can't ignore the impact of amputation concerns. This complication represents a very visceral fear for people with diabetes, and some HCPs have stopped prescribing Invokana altogether in favor of Lilly/BI's Jardiance (empagliflozin) and AZ's Farxiga (dapagliflozin) - as Dr. Jay Skyler said at CMHC 2017, "why deal with this concern if you don't have to?" That said, the dominant commentary we've heard from thought leaders is that amputation risk is manageable with careful patient selection and monitoring. Experts also emphasize that the rate of heart disease far outpaces the rate of amputations in a diabetes patient population, and some (Dr. Anne Peters, Ms. Virginia Valentine) have pointed out that Invokana is more effective than Jardiance in terms of glucose-lowering and weight loss. Regardless, Jardiance had a much better year financially than Invokana, on the strength of its new CV indication; franchise sales more than doubled YOY in 3Q17 ($127 million), 4Q17 ($436 million), and 2017 ($1.4 billion). Note that we estimate total global sales for the Jardiance franchise, since only Lilly's share (and not BI's) is reported publically. We've based our calculations on the assumption that Lilly's portion represents ~33%, given that BI listed global net sales for the franchise at €165 million, or ~$183 million, in a 2015 diabetes update, the same year in which Lilly collected $60 million in full year franchise revenue (this may be quite incorrect!). Rounding things out, AZ's Farxiga experienced solid but lower growth compared to Jardiance, with revenue rising 30% YOY in 3Q17 to $285 million and 39% YOY in 4Q17 to $332 million. Farxiga had its first blockbuster year in 2017, with $1.1 billion in sales, growing 29% over 2016. Ideally, we'd like to see the entire SGLT-2 inhibitor class growing at pace with Jardiance, and there's ample room for this: Equivalent to GLP-1s, only 7% of second-line diabetes prescriptions in the US go to SGLT-2 inhibitors. We'll have to wait-and-see if/when the Invokana business recovers (we do believe this is a question of "when" rather than "if"), and in the meantime, Merck/Pfizer's recently-launched Steglatro (ertugliflozin) franchise also holds exciting potential to stimulate underlying class growth if it receives investment from the two companies.

- **Market share by value and volume is shifting. As of 4Q17, Jardiance held 42% of the $1 billion market while Farxiga held 32% and Invokana held 16%.** This stands in stark contrast to the end of 2016, when Invokana held 44% of market share by value, followed by 28% for Farxiga and 27% for Jardiance. In terms of volume as well, Jardiance seems to be "stealing share" from Invokana against the backdrop of overall class growth. According to AZ's 4Q17 earnings presentation, Farxiga continues to lead in volume at 41% of total SGLT-2 prescriptions globally, followed by Jardiance with 35% and Invokana with 17%. Just two quarters earlier in 2Q17, this split was 40%/30%/22% respectively, suggesting that Farxiga is holding ground as Invokana share falls to Jardiance.
- **Merck/Pfizer launched Steglatro in January, adding a fourth SGLT-2 inhibitor to the US market. Ertugliflozin received final marketing authorization from EMA in late March, so European launch is also coming in 2018.** The ertugliflozin franchise includes standalone Steglatro plus fixed-dose combinations with DPP-4 inhibitor sitagliptin (Steglujan) and with metformin (Segluromet). It remains to be seen how Steglatro might shake up the SGLT-2 inhibitor class. We've been a bit underwhelmed by promotional efforts on the part of Merck and Pfizer so far, though it is admittedly early in the launch cycle. Notably, Merck/Pfizer have priced Steglatro lower than competitors: At our local CVS, the list price for Steglatro is $319 per month or ~$10.63/day vs. ~$17/day on average for the other SGLT-2s ($518/month for Jardiance, $517/month for Invokana, and $520/month for Farxiga). List price only means so much without considering insurance coverage and patient discounts, but we imagine $6/day of cost-savings ($180/month) could make Steglatro a very attractive option in payers' eyes. On the other hand, it's possible that this price will rise as Steglatro makes its way onto formularies and Merck/Pfizer begin paying rebates to PBMs/payers. We'll be watching closely as these pricing dynamics play out, and at the very least, we expect ertugliflozin to grow the SGLT-2 class overall

SGLT-2 Inhibitor Sales (1Q13-4Q17)



- **AZ's DECLARE trial for Farxiga will report in 2H18, and the implications of this third SGLT-2 CVOT are tremendous.** Is cardioprotection a class effect of SGLT-2 inhibitors? Are amputations a class effect? Is there potential for SGLT-2 therapy to reduce CV risk in a primary prevention population (~60% of DECLARE participants had no prior CV events at baseline)? AZ management has mentioned expanding market "breadth" for Farxiga, suggesting that positive DECLARE results could support a broader CV indication - Jardiance is only approved to reduce CV death in diabetes patients with *established CV disease*. We're noticing more commentary/criticism from diabetes thought leaders of late on the generalizability of CVOT results, since most of these outcomes studies feature an enriched study population (i.e. patients who are "more sick" to drive event rate). At ACC 2018, we saw an analysis showing that fewer than half of patients with diabetes would qualify for any SGLT-2 inhibitor CVOT - DECLARE is certainly the most inclusive, compared to CANVAS and EMPA-REG OUTCOME. In addition to investigating primary prevention, DECLARE has a co-primary endpoint that includes heart failure - a first for any diabetes CVOT. The heart failure benefit of SGLT-2s has emerged as a surprise upside following CANVAS and EMPA-REG; DECLARE could potentially support a first-in-class indication on this front. Further down the line, VERTIS-CV for Merck/Pfizer's Steglatro is expected to complete in October 2019. A CV indication for Invokana is currently under review at FDA, with a decision expected in late 2018.
- **SGLT-2 inhibitors are also being investigated for new possible indications, including heart failure, CKD, and type 1 diabetes, which could greatly expand the market.** Lilly/BI are conducting the EMPEROR HF program of Jardiance in chronic heart failure with or without diabetes (two studies focusing on HFpEF and HFrEF are expected to complete in June 2020). Additionally, Lilly/BI will initiate a program of Jardiance in CKD later this year. AZ has launched the Dapa-HF and Dapa-CKD studies, also in patients with or without diabetes, expected to complete in December 2019 and November 2020, respectively. J&J's CREDENCE trial of Invokana in patients with DKD should read out in 2H19. Across the board, the cardiology community seems particularly enthusiastic about the potential for SGLT-2 inhibitors to treat CV disease, especially heart failure, and we're eagerly anticipating results from these programs. On the type 1 front, AZ promptly submitted dapagliflozin (Farxiga) for type 1 diabetes to the EMA after DEPICT 1 data was presented at EASD 2017; management has promised DEPICT 1 trial extension results (52-week data) and DEPICT 2 results later in 2018. Lilly/BI will also report phase 3 EASE results for Jardiance in type 1 this year. Finally, Lexicon/Sanofi have submitted SGLT-1/2 dual inhibitor sotagliflozin for type 1 diabetes to FDA and EMA. Theoretically, these drugs (sotagliflozin, dapagliflozin) could be available to treat type 1 in 2019.

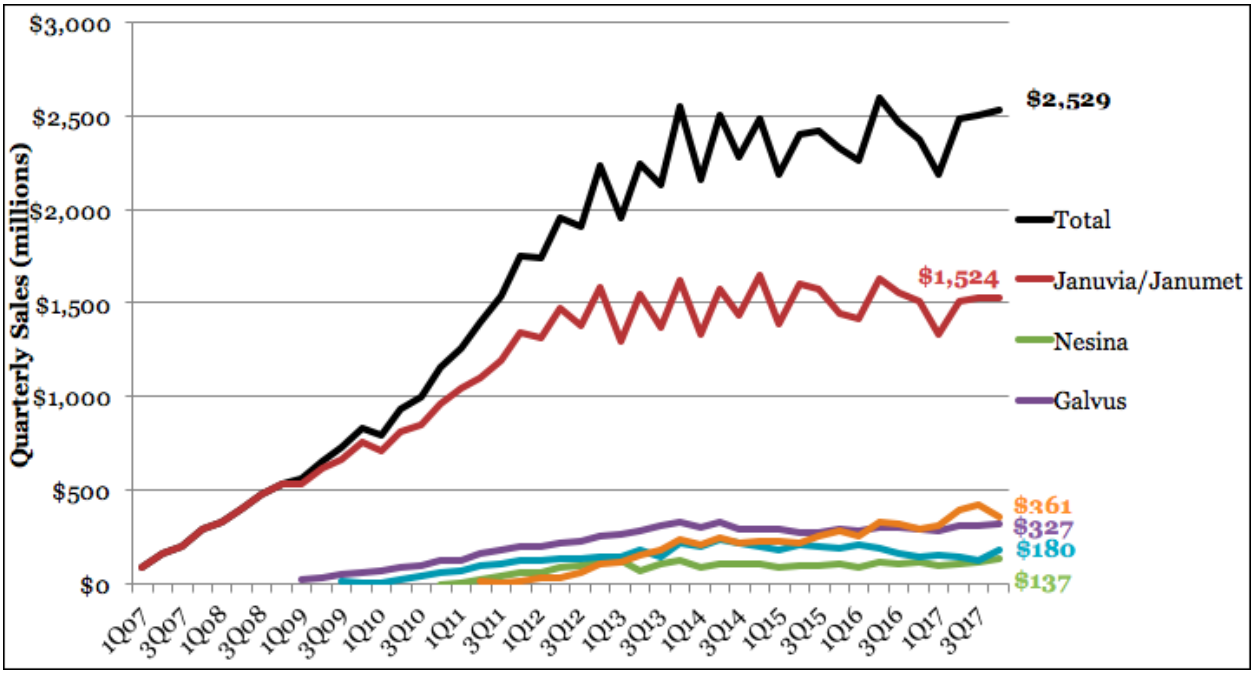
DPP-4 Inhibitors

DPP-4 Inhibitors Flat at $9.7 Billion in 2017; ~5% YOY Growth in 2H17 Balances ~4% YOY Decline in 1H17; Market Hovering Around $2.5 Billion in Quarterly Sales in the Face of Pricing Pressure

- **Sales of DPP-4 inhibitors were flat YOY in 2017 at $9.7 billion. The market grew 2% YOY to $2.5 billion in 3Q17, and rose 7% YOY to $2.5 billion in 4Q17.** This modest growth in the second half of the year was a rebound from 3% and 4% YOY drops in 1Q17 and 2Q17 to $2.2 billion and $2.5 billion, respectively. Since 2013, the DPP-4 market has fluctuated between $2.1-$2.6 billion quarterly, and 2017 was a characteristic year in this sense. That said, at $9.7 billion in revenue for the year, DPP-4 inhibitors are surpassed only by the overall insulin market in sales and they rival the $9.9 billion in pooled sales from all basal insulin analogs in 2017. DPP-4s captured nearly 50% of the branded diabetes drug market excluding insulin in 2H17 (49% in 3Q, 46% in 4Q, and 48% in 2017 overall). They drove a respectable 6% of growth in the market for diabetes drugs excluding insulin in 3Q17 (this market as a whole grew 4% YOY to $5.1 billion) and an impressive 17% of this growth in 4Q17 (when the market grew 10% YOY to hit $5.5 billion). Zooming out to the entire diabetes industry, spanning all major drugs and devices, DPP-4 inhibitors contributed a 5% share of growth in 3Q17 (market +7% YOY to $12.6 billion) and a 14% share of growth in 4Q17 (market +7% YOY to $13.4 billion). This all underscores that DPP-4 inhibitors remain a substantial piece of the diabetes industry, and these convenient oral agents continue to serve an important purpose in diabetes care. Despite US pricing pressure and competition from SGLT-2s and GLP-1s, pooled DPP-4 revenue has held more or less steady. We consider this a particularly impressive performance considering DPP-4s don't carry any (stated) CV benefit and usually offer less effective glucose-lowering than SGLT-2s or GLP-1s; on the other hand, we do understand they are particularly helpful to patients early in disease progression and are, to our understanding, more affordable than other branded drugs. DPP-4 inhibitors are, of course, also highly-familiar medicines within the diabetes community, and they boast a strong safety/tolerability profile. We're curious about hard TRx numbers, which no company has provided in recent history. During Merck's 3Q17 update, management shared that global prescription volume for Januvia was on the rise despite a 2% drop in franchise revenue that quarter; they forecast continued volume growth for Januvia and Janumet, especially outside the US, which should help offset US pricing pressure (higher rebates to PBMs/payers, higher patient discounts, and segment mix favoring Medicaid).
- **Merck's Januvia (sitagliptin) franchise was once again the frontrunner within the DPP-4 inhibitor class in 2H17.** As of 4Q17, Januvia and Janumet together reflected 60% of the market by value ($1.5 billion out of $2.5 billion total). Lilly/BI's Tradjenta (linagliptin) followed with $361 million reflecting 14% of pooled sales. Novartis' Galvus (vildagliptin) posted $327 million in 4Q17 and captured 13% of pooled sales, while AZ's Onglyza (saxagliptin) posted $180 million and took home 7% and Takeda's Nesina (alogliptin) posted $137 million and claimed 5%. These value share estimates were similar in 3Q17, when Merck held 61% with Januvia, Lilly/BI held 17% with Tradjenta, Novartis held 12% with Galvus, AZ held 5% with Onglyza, and Takeda held 5% with Nesina. In fact, this split of the DPP-4 inhibitor market by product has been relatively constant for at least six consecutive quarters now - pooled class sales aren't moving drastically quarter-to-quarter, and neither is the division of market share by value. Importantly, this analysis is based on our calculations for total Tradjenta franchise revenue: Only Lilly's sales are reported publically, and we approximate Lilly's share at ~36% of total worldwide revenue. This is based on Lilly's reported Tradjenta revenue of $357 million in 2015, the same year that BI reported global net sales for Tradjenta at €909 million, or ~$1 billion, in a special diabetes update.
- **Throughout 2017, we noticed increasing discussion on the role of DPP-4 inhibitors in treatment algorithms, particularly at a time when other diabetes therapies offer cardioprotection.** For the foreseeable future, DPP-4s will certainly make up a substantial fraction

of the diabetes drug market. These agents are often regarded as the most tolerated drug class, offering an incredibly strong safety profile and decent A1c-lowering - especially, again, for those taking it early in their disease progression. Moreover, DPP-4s have been widely defended as an ideal option for patients who are older, who have renal impairment, or who are early in the course of disease. At the same time, they offer no weight loss and no cardioprotection - two important clinical benefits that patients get when they take an SGLT-2 inhibitor or a GLP-1 agonist. Indeed, for every defense we hear of DPP-4s, we hear someone arguing for their de-prioritization. Dr. Jay Skyler said at Keystone 2017 that he favors SGLT-2s or GLP-1s for his patients with type 2 diabetes. Just recently at ENDO 2018, Dr. Steve Nissen called DPP-4s the least cost-effective diabetes treatment out there; he pointed out that they're not all-that-much cheaper than SGLT-2s or GLP-1s, are less efficient in lowering blood glucose, and come with none of the weight loss, CV, or renal benefits. Concerns around CV safety - specifically, heart failure - also persist with some around DPP-4 inhibitors, though we don't believe this is a class effect (and believe this is not a concern for most). The FDA added a warning for heart failure on the Januvia, Nesina, and Tradjenta labels in 2017, despite the fact that most consider the signal unique to Onglyza and the SAVOR-TIMI trial. The CAROLINA and CARMELINA CVOTs for Tradjenta haven't even reported yet, while the hazard ratio on heart failure hospitalization in the TECOS trial for Januvia was resoundingly neutral at 1.00. Hospitalization for heart failure trended in the wrong direction in Takeda's EXAMINE trial for Nesina, but this finding did not reach statistical significance. The sense we've gotten is that most thought leaders use DPP-4 inhibitors without reservation in people without a history of heart failure. We certainly expect this class to do very well at high prescription volume for some time to come - it is, of course, still the largest class with the most profitability (not necessarily the highest ratio).

DPP-4 Inhibitor Sales (1Q07-4Q17)



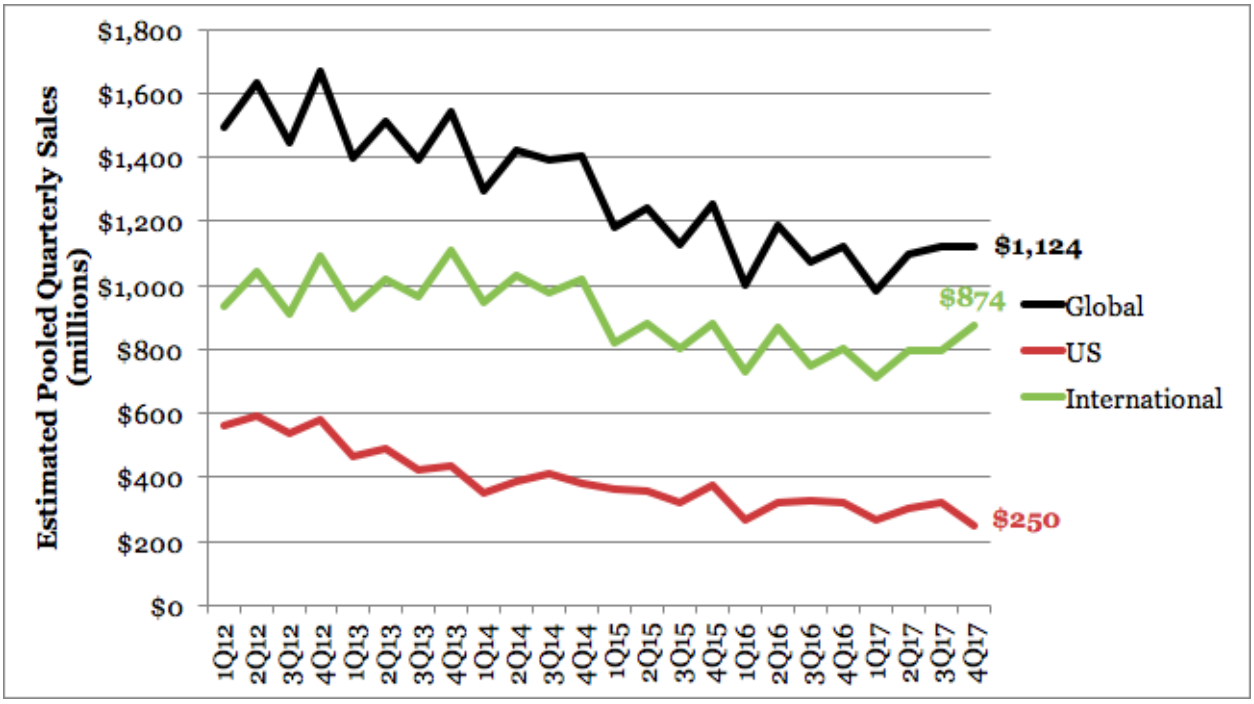
Diabetes Technology

BGM

"Big Three" BGM 2017 Estimated Sales of $4.3 Billion Decline 2% YOY; Two Consecutive Quarters of International YOY Growth

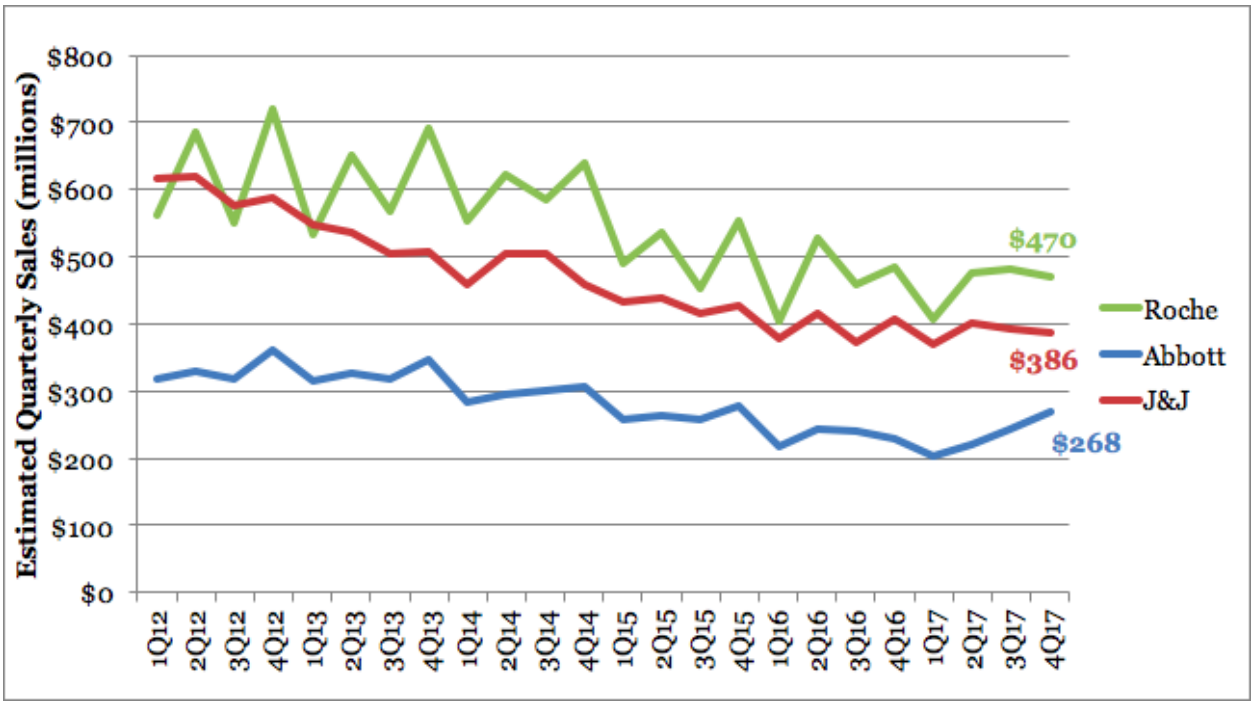
- **Pooled global revenue for the "Big Three" BGM companies (Roche, J&J, and Abbott) totaled an estimated ~$4.3 billion for 2017, down 2% YOY on an easy comparison to a 9% decline in 2016.** Pooled sales grew 4% YOY to $1.1 billion in 3Q17, and remained flat YOY at $1.1 billion in 4Q17. Although BGM revenue has been on a steady decline since its peak in 2011, there are sign of recovery, particularly in the international markets, which saw positive YOY growth in the past two quarters - a first since 3Q14 (though both came on easy comparisons to the prior year). The US remains quite challenged in our model - see the graph below. By our estimates, global Big Three BGM sales have declined ~33% between 4Q12 and 4Q17, with Roche the most challenged (-35%) and J&J not far behind (-34%). Abbott's BGM sales have been slightly more resilient to competitive BGM pricing and CMS's Competitive Bidding program, declining 26% since 4Q12, although this was from a much lower base. (It is also possible that we are under-estimating FreeStyle Libre's contribution to Abbott's overall revenue (see the CGM section), painting a more favorable picture for the company's traditional BGM line.)
    - **These BGM figures are highly estimated for Abbott, J&J, and Roche, and do not include figures for Ascensia (now private under Panasonic/KKR).** In addition to BGM, Abbott has FreeStyle Libre CGM, J&J has Animas pumps (although given the Animas exit in October, we've estimated that J&J earns very little from its pump business), and Roche has Accu-Chek pumps and revenue from Senseonics distribution, among other revenue sources (none of the companies break out sales by segment). See the CGM and pumps section for specifics on our assumptions. BGM growth and sales might look better or worse than what we've reported here, depending on the accuracy of our assumptions within the other business segments.

Pooled BGM Sales by Geography, Estimated, Big Three - Roche, Abbott, J&J (1Q12-4Q17)



- **International BGM sales totaled $3.2 billion in 2017, up 1% YOY on an easy comparison to a 7% YOY decline in 2016.** This is the first annual growth reported internationally since 2013, the last time the OUS BGM market surpassed ~$4.0 billion in revenue. OUS revenue totaled $796 million (+7% YOY) in 3Q17 and $874 million (+9% YOY) in 4Q17, marking two encouraging consecutive quarters of positive YOY growth - the first time international sales have grown YOY since 3Q14. We estimate that all members of the Big Three reported international growth in 3Q17 and 4Q17, with J&J sales rising 12% and 8%, Abbott sales rising 10% and 24%, and Roche sales rising 13% and 14%. It's important to note that for all three companies, these performances came against easy comparisons, and the growth for all three could reflect under-estimations of contributions from sensors/pumps.
- **US BGM sales totaled $1.1 billion in 2017, down 7% YOY on an easy comparison to 13% YOY declines in 2016.** This was the sixth consecutive year of annual declines for the US BGM segment, underscoring the devastation imparted by CMS's Competitive Bidding (and likely some pressure in BGM as high-frequency strips users move to CGM). 3Q17 US revenue totaled $323 million, down 1% YOY on a modest comparison to 2% growth in 3Q16. US 4Q17 sales of $250 million declined a whopping 22% YOY, primarily driven by YOY declines of 24% and 53% from J&J and Roche respectively (it is possible that these estimates are off in magnitude, depending on their pump businesses). While J&J reported US declines in both 3Q17 (-2% YOY) and 4Q17 (-24% YOY), Abbott and Roche each had one negative and one positive quarter: Abbott reported 5% YOY growth in 4Q17 (but -13% in 3Q17), and Roche reported 18% YOY growth in 3Q17 (but -53% in 4Q17 against -44% in 4Q16!).

BGM Sales by Company, Estimated, Big Three - Roche, Abbott, J&J (1Q12-4Q17)



- **We estimate Roche's 2017 BGM sales were ~$1.8 billion, down 2% YOY against an easy comparison to an 8% decline in 2016.** Revenue rose an estimated 5% YOY in 3Q17 (~$483 million) followed by a 3% YOY decline in 4Q17 (~$470 million).
- **We pegged J&J's 2017 BGM sales at ~$1.5-$1.6 billion, down ~2% YOY in 2017.** This performance comes against an easy comparison to an 8% decline in 2016. LifeScan BGM sales were an estimated ~$393 million in 3Q17 (+5% YOY) and ~$386 million in 4Q17 (-5% YOY). We have modeled a very significant decline in Animas revenue; see the pump section below for more.

- **Estimated Abbott BGM sales in 2017 remained flat YOY at ~$934 million against an easy comparison to a 12% decline in 2016.** Revenue of ~$243 million rose 1% YOY in 3Q17, but saw very promising 17% YOY growth in 4Q17, with sales rising to $268 million. We estimated FreeStyle Libre sales at ~$480 million in 2017, more than doubling YOY.
- **The BGM market remains challenging, especially in the US.** CMS's controversial Competitive Bidding Program is partially responsible for consistent softening in US sales, although competitive dynamics, higher CGM adoption in high-frequency users, and broader use of glycemic-dependent agents (with much lower risk of hypoglycemia) are presumably also playing a role. What is the future of traditional BGM? Can the Big Three and others (e.g., Ascensia) re-calibrate their business models to accommodate the harsh pricing landscape and rising use of CGM? As more CGM systems with combinations of accuracy, user-friendliness, cost-effectiveness, solid form factor, and factory-calibration come to market (namely, Abbott's FreeStyle Libre, newly FDA-approved Dexcom G6, but also Medtronic's standalone Guardian Connect mobile CGM and Senseonics's implantable Eversense), traditional BGM companies will need to move beyond selling strips to selling outcomes - with strips as one part of a package. Thus far, Abbott has responded to (and anticipated) the pressure by shifting focus to FreeStyle Libre (we can't remember the last time "BGM" was even uttered on a quarterly call), while Roche has taken a digital approach by acquiring mySugr and forging a strong bond with Senseonics. J&J is getting out of the BGM business entirely, announcing plans in March to sell LifeScan for ~$2.1 billion to Platinum Equity. Current LifeScan President Valerie Asbury will continue leading the business, and the goal is to "create a global standalone business and set the stage for continued investment in growth and innovation." It seems like a similar model to Panasonic's Ascensia (Bayer Diabetes)?
- **Moving forward, the difference-making innovation in glucose monitoring will need to be more focused *around* devices and improving access to connected devices.** Glucose meters have reached the point where they are highly accurate, fairly user-friendly (apart from the unavoidable finger-prick), and connected in many cases. We see a lot of potential for new business and service models that provide BGM as part of a broader outcomes-driven program that combines many tools - glucose monitoring, coaching, decision support apps, education, etc. Though it is moving slowly, the field is inevitably shifting toward value/$ - how can glucose monitoring be deployed more intelligently along with other tools in a population? We have seen shades of this approach from smaller players - going at-risk by taking on patients and getting paid for outcomes - from mySugr (acquired by Roche), Livongo, One Drop, who all offer coaching and unlimited strips for a subscription fee (direct-to-consumer), but also go at-risk to some degree with employers/ payers. Outside of BGM, Onduo, Virta, Medtronic's Turning Point Program, Dexcom/UHC/Fitbit, and Glooko/Fit4D have all thrown their hats into the "connected care" ring. What will truly drive outcomes at scale? There are many unanswered questions about the best way to support different kinds of patients with different coaching styles, frequency of engagement, type of advice given, and how and when to deploy different drugs and technologies.
    - **On the access point, we remain struck by low access to BGM and strips in developing nations - how can this shortage be mitigated in a business-friendly manner?** See our report from March on the East African Diabetes Study Group Congress for just one example from Rwanda. Many of these countries don't have national healthcare, and if they do, strips are often not covered. A global fund of sorts could be a solution, but we also wonder about alternative approaches, such as social bonds, where individuals and organizations can invest in the health of others, and reap returns, either through shared savings or increased productivity.
- **If LifeScan does indeed change hands, how will that impact the BGM landscape?** Despite struggles of late, the LifeScan business still brought in well over a billion dollars in 2017. Assuming the deal goes through, what will Platinum Equity do with the business? Will Platinum - who lacks significant healthcare experience - invest in a digital ecosystem (possibly following Roche's lead and acquiring One Drop, Livongo, or Glooko), push forward on making the OneTouch

Reveal app the center of the diabetes business, and will a Bluetooth-enabled Verio Flex BGM still launch with WellDoc BlueStar integration? Would delivering BGM at low cost to markets too immature for CGM at the moment be a priority? Get our deep dive on Platinum/J&J here.

- **With Abbott and Dexcom now factory-calibrated, will the traditional BGM field see even fiercer pressure?** While patients will still need to have BGM and strips on hand to test intermittently (e.g., to optionally calibrate Dexcom's G6 or in some instances with FreeStyle Libre), we do wonder to what degree BGM sales will be further affected moving forward. The impact will likely be small at first, but as factory-calibrated CGMs get more cost-effective and smaller and more high-frequency testers (both type 1 and type 2) adopt them, we imagine the dent might grow over time.

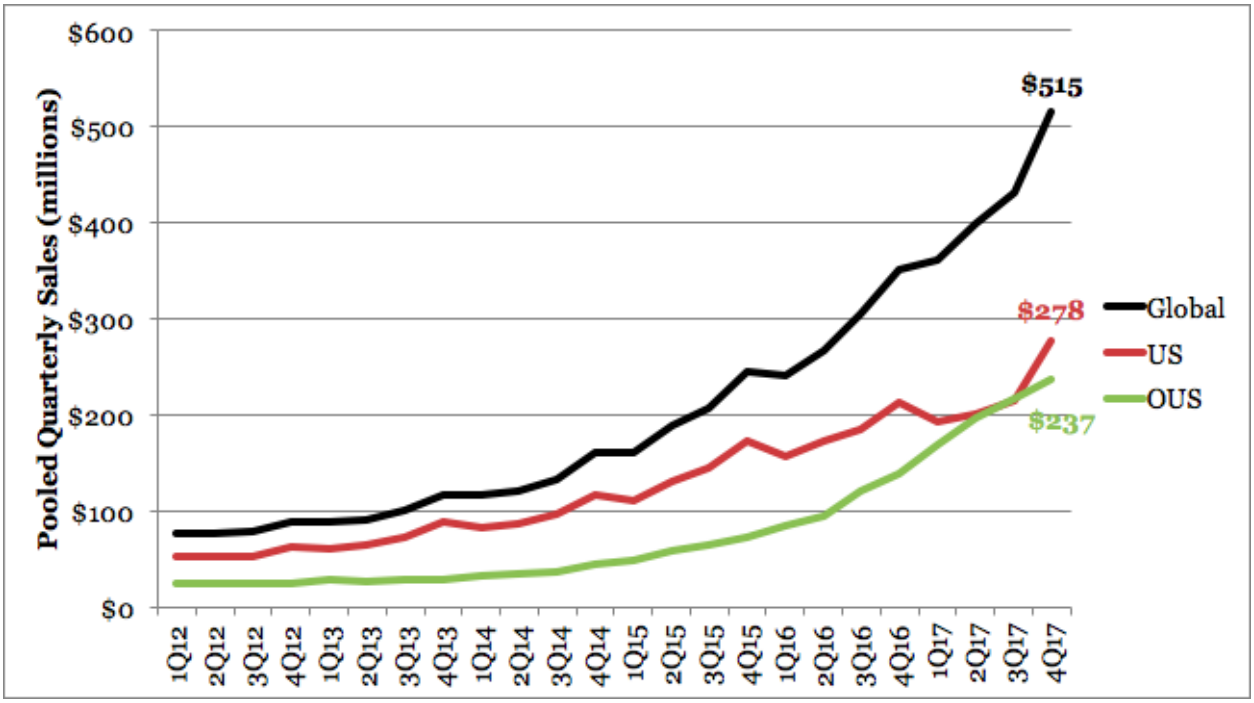
CGM

Worldwide sales of ~$1.7 billion in 2017, rising 46% YOY; 1st ever quarter crossing $500 million! OUS sales drive ~70% of category growth in 2017

By our estimates, the worldwide CGM market grew to ~$1.7 billion in 2017, up an impressive 46% YOY from the previous record in 2016 (~$1.2 billion, +45% YOY). This represents faster growth from a much higher base of sales, a testament to international momentum for CGM (driving a record ~70% of the category's 2017 growth!); improved products; global reimbursement wins (Medicare, UK, France, Germany, Japan); growing studies and real-world Big Data (ATTD 2018: Abbott, Dexcom, Medtronic); and rising clinician enthusiasm alongside the Beyond-A1c movement.

- **We estimate global CGM sales were ~$432 million in 3Q17 (up ~41% YOY) and a record-smashing ~$515 million in 4Q17 (up ~46% YOY)** - the latter represents a huge milestone for CGM, crossing half a billion in quarterly sales for the first time in our model.
- **By company, we estimate Abbott provided ~50% of the CGM category's 2017 growth, Dexcom provided ~27%, Medtronic provided ~22%, and Senseonics provided ~1%.** Our model includes Dexcom's reported sales, our best estimates for Medtronic and Abbott's FreeStyle Libre (clarified below), and Senseonics. This is the second roundup where we've included sales estimates for Abbott's FreeStyle Libre in the CGM category, which we pegged at roughly ~$130 million in 3Q17 and ~$145 million in 4Q17 - assumptions are below, and we caution these might over- or underestimate FreeStyle Libre's actual global sales. Given Libre's enormous user base (~450,000 as of 4Q17), it is clear that the factory-calibrated sensor is really growing the continuous glucose sensor market outside the US. (Our CGM model shown below is revised to include historical sales estimates back to Libre's launch in Europe in fall 2014.) Meanwhile, Medtronic told us in mid-2017 that its CGM sales are now ~25% of its Diabetes sales, up from ~20% two years ago - this too shows category expansion. We include a more detailed company-by-company analysis below.

CGM Sales: Worldwide, US, and International (1Q12-4Q17) - Pooled Dexcom, Abbott (estimated), Medtronic (estimated), Senseonics



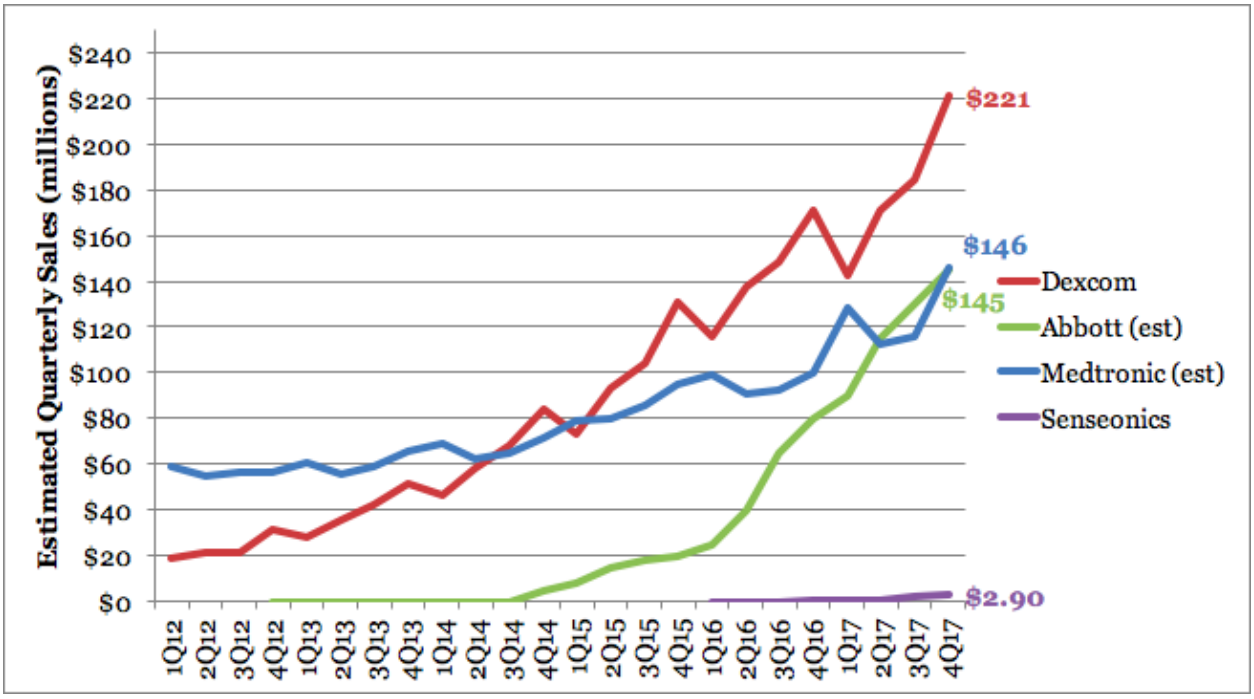
- **International CGM growth was the category's major story of 2017: we estimate a record-high ~48% of CGM sales came from outside the US in 2017 (~$820 million), growing ~86% YOY and driving an impressive ~70% of the category's growth.** In comparison, US CGM sales were an estimated ~$887 million in 2017, rising a slower 22% YOY. Abbott carried the international CGM market by our estimates, driving ~71% of the OUS CGM market's growth on 2017 estimated sales of ~$480 million. In the US, Dexcom supplied the majority (61%) of category growth, though at a much lower level than in 2016 (when it supplied 90% of US growth). Assuming our sales estimates for Abbott's FreeStyle Libre and Medtronic's CGM are in the ballpark, it is remarkable that the US/OUS geographies are now almost equal in terms of estimated sales - in 2016, by contrast, we estimated US sales were nearly ~$300 million higher! (Note the chart above and compare the US/OUS gap between 4Q16 and 4Q17.) This international momentum reflects: (i) strong adoption of Abbott's FreeStyle Libre in 40+ countries, which is adding ~50,000 users per quarter; (ii) Dexcom's much stronger 61% international growth in 2017 vs. more modest 20% growth in the US; (iii) Medtronic Diabetes' stronger international vs. US growth throughout 2017; (iv) no availability of FreeStyle Libre in the US until the last month of 2017; (v) no availability of Medtronic's Guardian Connect in the US (launching this May-July) and limited availability of the Guardian Sensor 3/670G throughout 2017.
    - **We expect the US to see higher growth in 2018, given:** FreeStyle Libre's (real-time) US launch ramping up; Dexcom launching the factory-calibrated G6 in 2Q18; and Medtronic launching its own standalone Guardian Connect CGM/Sugar.IQ app in May-July, along with expanding the MiniMed 670G/Guardian Sensor 3 launch. Senseonics may also launch in the US in 2018, depending on when FDA approval comes through following the positive March 29 advisory committee for Eversense. We're very excited for four outstanding sensors to be widely available in the US, along with access to improve - even in type 1 diabetes at the very best US centers, CGM is still reaching an estimated 24% of type 1s (per Dr. Roy Beck's T1D Exchange talk last fall).
- **We estimate CGM may now be used by roughly 0.8-1 million people globally, with the vast majority living with type 1 diabetes.** Though each company likely defines a "user" differently, the table below highlights what we've heard publicly about user base size for Abbott (~450,000), Dexcom (270,000+), and Senseonics (~2,000). We've also included our best guess for

Medtronic's CGM user base, given ~25% of its sales from CGM and likely similar per-patient revenue to Dexcom. We caution that the Medtronic and Abbott rows are highly estimated, but represent our best guesses.

Company	2017 Sales YOY growth from 2016	Users** at End of 2017 YOY growth from 2016	Revenue per user per year
Dexcom	$719 million +25%	>270,000 +35%	~$2,700
Medtronic	~$502 million (est)* +31%	~185,000 (est)* +31% (est)*	~$2,700*
Abbott	~$480 million (est)* +128%	~450,000 +50%	~$1,100*
Senseonics	$6.4 million >1000%	~2,000 users >1000%	~$3,200
TOTAL CGM	**~$1.7 billion +46%**	**~900,000 users +40%**	**~$1,900**

*Close Concerns' estimates - figures for Abbott sales and Medtronic sales/user base could be off in magnitude.
** Companies likely categorize "users" differently, so these may not be directly comparable.

CGM Sales By Company (1Q12-4Q17) - Dexcom, Abbott (estimated), Medtronic (estimated), Senseonics



- **Dexcom's 2017 sales of $719 million rose 25% YOY, including US sales of $596 million (+20% YOY) and OUS sales of $122 million (+61% YOY).** The OUS business had a "breakout year" and drove a record 38% of 2017 growth. The clear sales highlight of the year was in 4Q17, when sales hit a record $221 million, rising 29% YOY on US momentum and smashing the previous record from 3Q17 ($185 million). 2018 sales are expected to be $830-$850 million, a softer 16%-19% YOY rise over 2017. The business' key indicators - sensor volumes, OUS revenues, and patient base

growth - are expected to exceed 20% growth in 2018, again outpacing revenue growth. We would not be surprised to see Dexcom exceed sales guidance, given the much-earlier-than-expected March 27 clearance of G6 with factory calibration; a US launch is expected late in 2Q18, presumably with a big coming-out party at ADA. Dexcom hit a regulatory homerun with G6, as the 10-day wear sensor is down-classified to 510(k) as an "integrated CGM" (iCGM) with a focus on interoperability. The FDA has published special controls for iCGM systems, including clear accuracy benchmarks that Abbott and Medtronic do not appear to meet at this time - see our deep dive here. Read our Dexcom 4Q17 report.

- **We estimate worldwide sales of Abbott's FreeStyle Libre were ~$480 million in 2017, more than doubling year over year.** This included ~$130 million in 3Q17 sales and ~$145 million in 4Q17 sales. These sales figures reflect our best estimates based on a number of assumptions - many of which could be incorrect. We detail our thinking below, followed by a table with the past seven quarters of data we've used to inform our model. It's been excellent to see the success of this well-priced, easy to prescribe, easy to order, and easy to use product. We can't wait to see how Libre real-time fares in the US in 2018 with the slight FDA approval modifications (10-day wear, 12-hour warmup, prescription only), especially once G6 is on the market with competitive factory calibration. FreeStyle Libre is launching into a more competitive/reimbursed market than it did in Europe in 2014, meaning adoption could be more gradual stateside. Read our Abbott 4Q17 report.
    - **User base (~450,000):** We've used the publicly announced global FreeStyle Libre user base figures when possible. Per the 4Q17 call, CEO Miles White said FreeStyle Libre was adding 50,000 users per quarter, implying a base of ~450,000 users at the end of the year. The last "official" update came in October, when Abbott said there were over 400,000 FreeStyle Libre customers worldwide.
    - **Pricing:** We're using flat Libre sensor pricing of ~$120 per month, which obviously does not account for discounts, different geographies/currencies, payer relationships, net pricing vs. retail price, etc. We're also excluding one-time reader sales of ~$60 each.
    - **Utilization:** We're assuming that 100% Libre sensor utilization is unlikely - i.e., every user globally buying two sensors per month. Our model estimates 90% utilization, which would reflect the vast majority of users (but not all) wearing Libre 100% of the time. We then rounded the final revenue number up/down to the nearest $5 million increment, just to emphasize that these are *estimates* and far from exact. For instance, 450,000 users * $120/month * 3 months * 90% = $145.8 million, which we rounded to ~$145 million. This level of utilization is in line with what Insulet has reported in the past for the Omnipod, though obviously Libre could be different - lower utilization (e.g., 75%) would drive a lot less revenue.
    - **What we still don't know or haven't estimated:** How does Abbott define a "user" - are all of these people currently wearing and ordering FreeStyle Libre, or is this base those who meet broader conditions (e.g., have ordered from Abbott at least once)? If the latter, revenue would obviously be less. How widely used is FreeStyle Libre Pro, and does the worldwide "user" number include professional sensor wear? (We assume not, but aren't sure.) We're also unsure of how pricing differs (if at all) in cases where FreeStyle Libre is reimbursed - presumably Abbott receives less than $120/month in these cases. Last, we haven't accounted for sales from readers (~$60 each), though assume they are small.

	2Q16	3Q16	4Q16	1Q17	2Q17	3Q17	4Q17
FreeStyle Libre User Base	125,000	200,000	250,000	~300,000	~350,000	400,000	~450,000

Est sales in our model*	~$40 million	~$65 million	~$80 million	~$90 million	~$115 million	~$130 million	~$145 million

*Assumes ~90% utilization, $120 per month sensor pricing, rounded to nearest $5 million increment - this estimate rests on a number of assumptions that may be off in magnitude

- **We estimate Medtronic's worldwide CGM sales totaled ~$502 million in 2017, rising 31% YOY.** This included ~$116 million in 3Q17 (up ~25% YOY) and ~$146 million in 4Q17 (up ~46% YOY). Medtronic confirmed with us in October that roughly 25% of its Diabetes sales now come from CGM, up from 20% as of late 2015 - our model now assumes Medtronic's sales mix from CGM rose to 25% in 2017, with 15%-20% used in 2016 and 2015. The mix likely varies from quarter to quarter and by geography. Medtronic may also have flexibility on how it recognizes "CGM revenue," since the receiver is actually the pump - that could mean "CGM sales" over-represent sensor sales and active user base. Medtronic's estimated CGM sales seem to be growing nicely, but overall performance in 2017 was below expectations. Worldwide Medtronic Diabetes sales (pump+CGM) rose 5% YOY in 2017, including a modest 2% in the US - and this was with the company's most important pump+CGM launch (MiniMed 670G) ever. Sensor shortages were in large part responsible for the year's overall weakness, which started to improve in 4Q17 - Guardian Sensor 3 production was twice as high as in the prior quarter. The capacity improvement translated directly to improved Diabetes sales, which rose 17% YOY (including 15% in the US). Medtronic's sensor capacity improvement efforts are on track to meet "all" sensor demand by April 30, in line with previous expectations. With the FDA approval of Guardian Connect in March, we expect improved CGM growth through the rest of 2018. A limited launch of Guardian Connect and the IBM Watson-partnered Sugar.IQ app are expected in May-July, with broader availability in August-October. Read our Medtronic 4Q17 report and our subsequent coverage of Guardian Connect.
- **Senseonics 2017 sales came right in line with expectations: $6.4 million, up nearly 20x from $332,000 in 2016. As of the February call, Eversense has ~2,000 users, up 135% sequentially from 3Q17 - a faster ramp than we would have guessed.** Management guided for $18-$20 million in revenue for 2018 (tripling YOY), but remaining fairly conservative regarding the 2018 US contributions. Given the unanimous 8-0 votes in favor of approval two weeks ago, we are optimistic for an FDA approval near term - especially given Eversense's very strong accuracy. (Indeed, it is the only device, besides Dexcom G5/G6, that appears to meet FDA's accuracy standards for the new class of iCGM. That said, Eversense is currently under a PMA application, so Senseonics will have to re-submit to obtain 510(k) clearance for an iCGM indication.) At the FDA advisory committee, we were struck by the open public hearing, which shared a slew of positive comments on Eversense's novel features relative to current CGMs. As of February, Senseonics expected to be commercially ready for a US launch by mid-2018; official launch will of course depend on the FDA negotiations. The rollout of the Eversense XL 180-day version - which started in the UK in November and in Sweden in March - should significantly enhance the value proposition relative to current devices.

Insulin Pumps and Delivery Devices

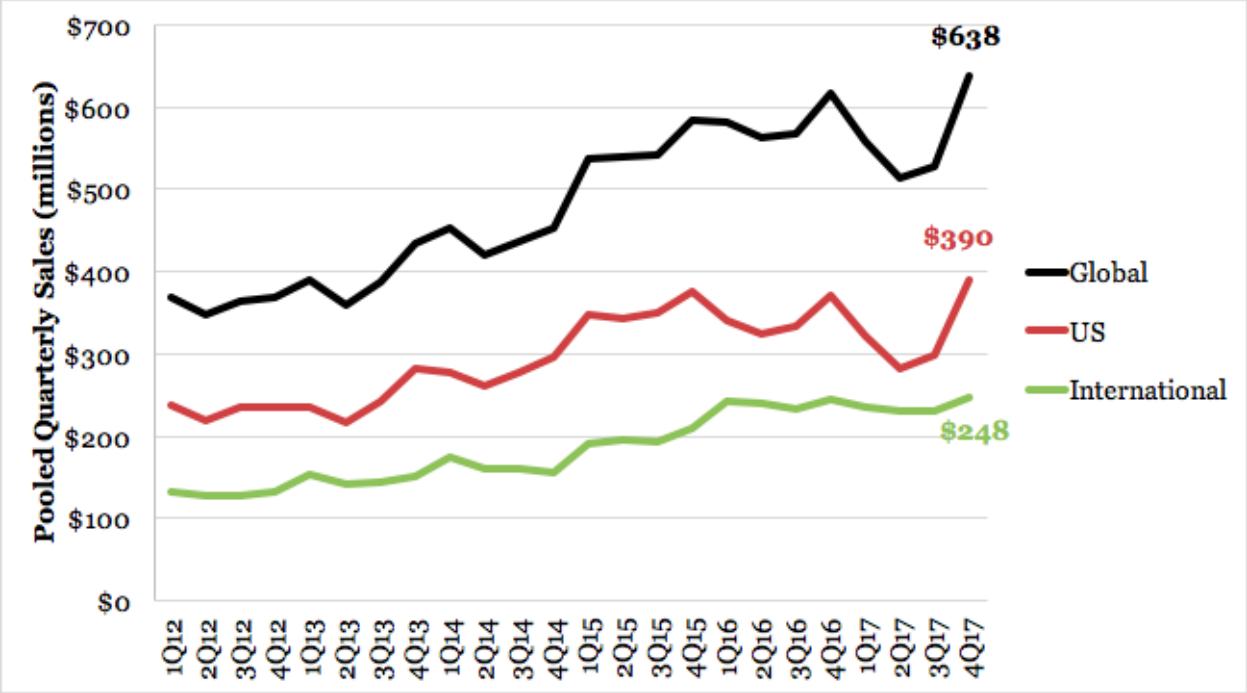
Sales Down 4% YOY on Challenging Year for Medtronic, Animas and Roche Exits; Strong 2017 for Insulet (86% share of category growth!) and Tandem

- **We estimate the insulin pump and delivery devices market fell ~4% in 2017 to ~$2.2 billion.** Pooled sales declined 7% to ~$529 million in 3Q17, followed by a rebound to ~3% growth in 4Q17 to ~$638 million. These estimates include sales from Medtronic (estimated), Insulet, Tandem, Animas (estimated), Roche (estimated), Valeritas, and Cellnovo - by our model Medtronic maintains a ~67% market share, up from ~66% in 2016. This is the first quarter in our model, which goes back to 2005, that estimated a yearly decline in pump industry revenue - 2016 was the peak for the field so far, pulling in ~$2.3 billion in yearly revenue. Most of the weakness in 2017 came in the first half

of the year (-6%), whereas the second half, buoyed by an industry-record $638 million fourth quarter, saw just a 1% decline.

- **For this roundup in particular, two factors drove our estimate of a decline in the pump market:** (i) rising Medtronic CGM sales from ~15%-20% of total sales previously to ~25% in 2017 (Medtronic confirmed this with us prior to our 1H17 roundup); and (ii) a significant modeled decline for Animas and Roche, given the former's closing and the latter's discontinuation of pump sales in the US. We'd caution that this category is weighted on these assumptions, which may be off in magnitude.

Pooled Insulin Pump Revenue, Estimated (1Q12 - 4Q17)

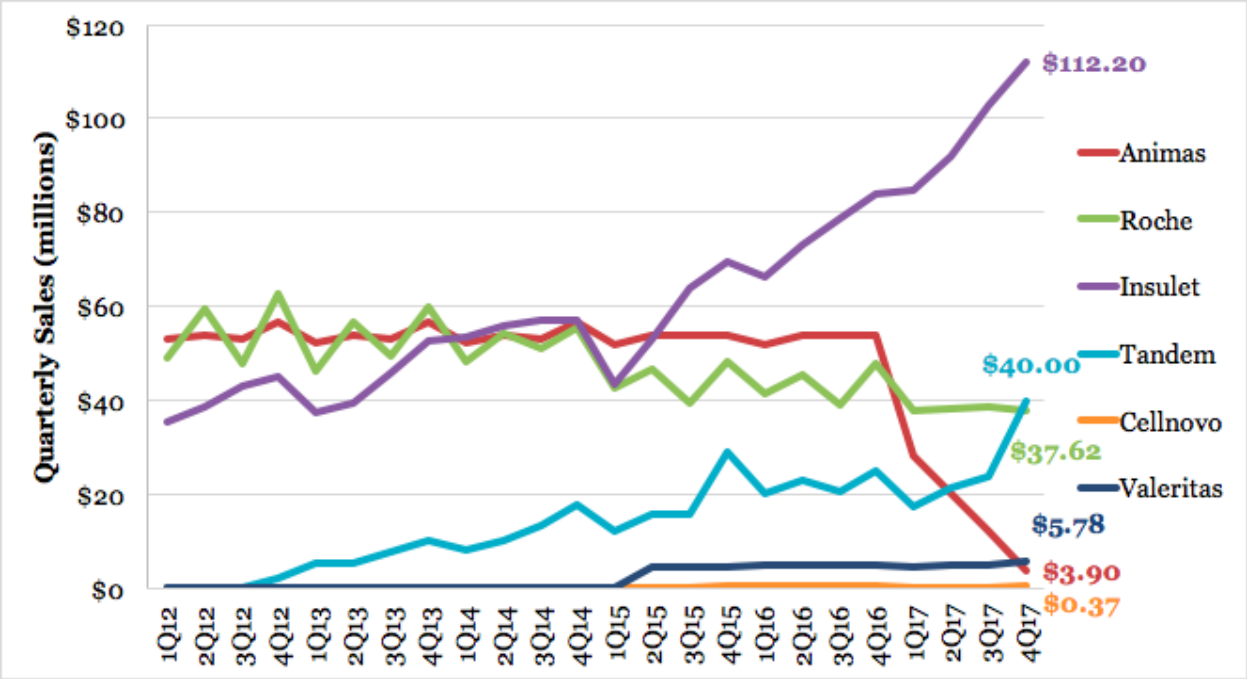


- **By our estimates, pump sales were sluggish both in the US and internationally in 2017. US sales declined a surprising ~6%** to ~$1.3 billion; OUS sales declined ~1% to ~$946 million.
  - **In the US, the big story was Medtronic, who saw a disappointing and unexpected ~5% sales decline for the US pump business in 2017** (estimated) - this came against an easy ~2% decline in 2016, and was even more surprising considering the first-to-market MiniMed 670G hybrid closed loop had its first full year on the market following September 2016 approval. Rewinding back to our 4Q16/2016 Roundup, we had expected a far bigger 2017 for pumps in the US, driven by Medtronic and the 670G. In retrospect, Medtronic's Guardian Sensor 3 CGM manufacturing capacity was not ready, and therefore, slowed the 670G rollout and the overall US pump category quite meaningfully. (Medtronic's 2Q17 guidance miss and revision from "10%-12%" to "1%-4%" growth was one of the largest we've ever seen.) But the US was not just a Medtronic story: Roche (discontinued sales in early 2017) and Animas (closed in October) contributed to a very difficult year too. Meanwhile, Insulet (+18%), Tandem (+16%), and Valeritas (+4%) also saw growth for the full year in 2017.
    - **The overall US pump market did show improvement in Q4,** as pump sales hit a record-high $390 million - Medtronic provided 38% of the growth (reflecting improved 670G/Guardian Sensor 3 capacity), followed by an outsized 32% share for Tandem, Insulet at 28%, and Valeritas at 2%.

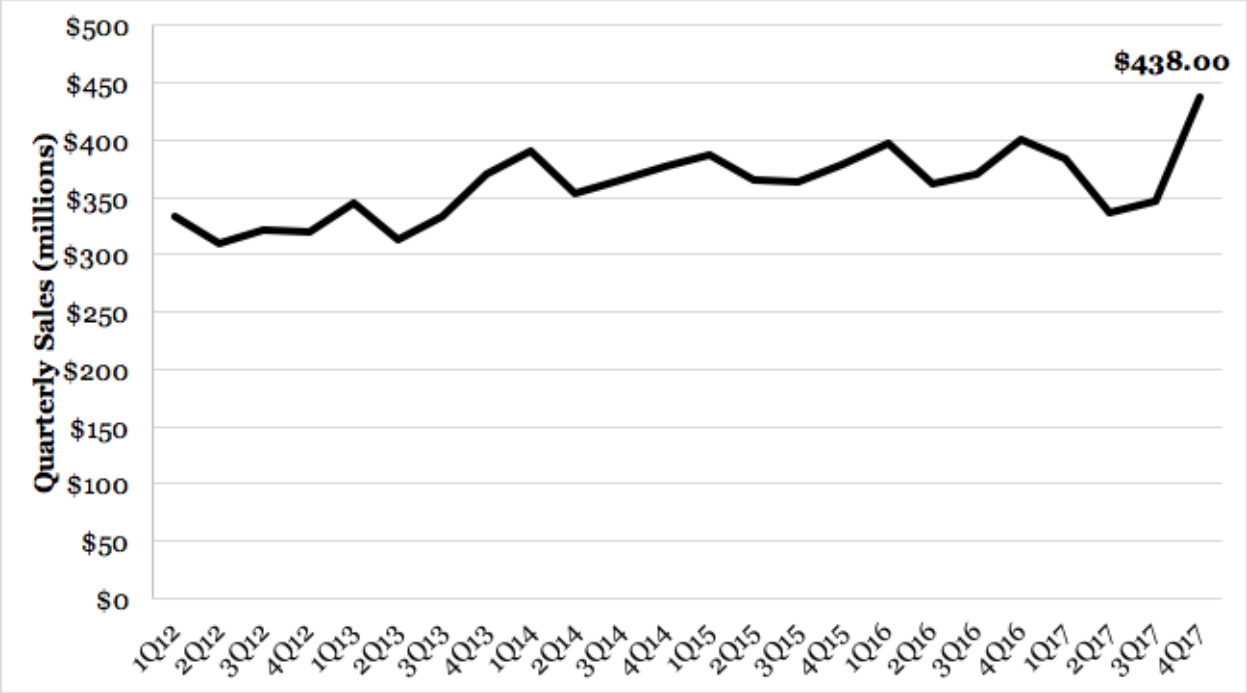
        - **Like CGM (see above), we expect pumps will fare better in the US in 2018, driven by new products.** Medtronic will finally have a full year of unconstrained MiniMed 670G/Guardian Sensor 3 launch (over 20,000 users as of February) now that sensor manufacturing capacity constraints are easing up; (ii) coming off a record 4Q17, Tandem plans to launch Basal-IQ Predictive Low Glucose Suspend this summer (currently under FDA review); and (iii) Insulet has guided for 16%-19% growth in US Omnipod sales ($316-$323 million), including 15%-18% US patient base growth.
    - **Outside the US, Insulet's international business was the clear highlight of 2017**: Omnipod sales rose an impressive 67% and hit nearly $120 million in revenue. We also estimate Roche (+7%) and Medtronic (+3%) saw growth internationally in 2017, though at lower levels than Insulet. Medtronic continues to tout "strong" 640G adoption (spearheading 12% OUS growth in 4Q17), and we expect the imminent launch of the 670G hybrid closed loop will help further (in the CE Mark process as of February, presumably setting up a European launch this year). On the international front, Tandem will begin sales OUS this year for the first time, starting with Canada and select European countries in 2H18. Insulet will also take over Omnipod distribution in Europe (from Ypsomed) in mid-2018 - the team expects 54%-62% growth in international Omnipod ($185-$194 million).

- **By company, Insulet was the pump field's major growth driver in 2017, propelling a remarkable 86% share of the category's growth. Tandem was second with a 14% share of growth,** and Valeritas rounded out the category with a 0.8% share of growth. (As noted above, our model has Medtronic, J&J, and Roche pumps with YOY sales declines in 2017.) This marks an impressive two-year stretch for Insulet, who also provided the majority of the pump industry's growth in 2016 at ~57%. We should note that Medtronic still holds nearly 70% of the estimated market by sales - how will it fare in 2018 with unconstrained capacity for the MiniMed 670G/ Guardian Sensor 3? How will Tandem's launch of Predictive Low Glucose Suspend compete with MiniMed 670G? How will Insulet fare with Omnipod Dash? How many patients will these companies scoop up this year with a four-year warranty, locking them in until 2022?! Meanwhile, how will patients weigh the AID pipelines across the board - how many will go for MiniMed 670G now, and how many will choose to wait for Tandem, Insulet, Bigfoot, Beta Bionics, and Lilly?

Insulin Pump Revenue by Company (minus Medtronic), Estimated (1Q12 - 4Q17)



Medtronic Pump Revenue, Estimated (1Q12 - 4Q17)



- **Medtronic's estimated worldwide insulin pump sales were ~$1.5 billion in 2017 (down ~1.5%).** Sales totaled ~$347 million (down ~6%) in 3Q17 and $438 million (up ~9%) in 4Q17. This estimate assumes that pumps account for ~75% of total revenue, as Medtronic told us in October. Prior to 2017, our model reflects the previous 80:20 pump:CGM split. Management expects "double digit" year-over-year growth in the upcoming quarter (February-April 2018) and for all of (May 2018-April 2019), off what should be relatively easy YoY comparisons. Read our Medtronic 4Q17 report.

- **Insulet's worldwide insulin pump sales were ~$392 million in 2017 (up ~30%).** Sales totaled ~$103 million (up ~30%) in 3Q17 and $112 million (up ~34%) in 4Q17. International Omnipod drove 50% of Insulet's 2017 sales growth, far outpacing its 26% share of total revenue. Insulet's worldwide installed base stood at ~140,000-145,000 active users at the end of 2017, reflecting ~33% YOY growth from 2016 (~105,000-110,000). For 2018, Insulet expects 15%-18% US patient base growth and softer 20%-25% base growth in Europe. 2018 guidance expects 16%-19% growth in US Omnipod sales ($316-$323 million) and 54%-62% growth in international Omnipod ($185-$194 million). This team almost always exceeds guidance, so we would not be surprised to see these numbers beaten. Read our Insulet 4Q17 report.
- **Tandem's worldwide insulin pump sales were ~$103 million in 2017 (up ~16%). This reflected a breakout 4Q17:** sales of $40 million (non-GAAP), rose 61% YOY and 69% sequentially on the t:slim X2/G5 launch. Tandem also saw record pump shipments of 6,950 rise 57% YOY and 80% sequentially in 4Q17. In 2017, pump shipments were 17,061, rising a more modest 1% YOY. A total of 68,890 pumps have been shipped cumulatively, and more than 50% of new patients are coming from MDI - a great sign Tandem is expanding the market. 2018 sales are expected to be $132-$140 million, implying accelerated 26% YOY growth at the midpoint. Tandem has many enablers in 2018, including the under-FDA-review Basal-IQ predictive low glucose suspend (Summer 2018 launch), commencing international sales in Canada and Europe, and a mobile app (2H18 launch). The company also believes it has enough financial resources to reach cash-flow breakeven in 2H19. Read our Tandem 4Q17 report.
- **We have modeled a significant decline in Animas's estimated worldwide insulin pump sales.** Our model has Animas sales at ~$64 million in 2017, down ~70%. We estimate that sales totaled ~$12 million (down ~78%) in 3Q17 and ~$4 million (down ~93%) in 4Q17. Animas closed its doors in October, but existing revenue flow estimates presumably reflect some continued supplies and service for existing customers (especially outside the US). There were ~90,000 worldwide customers as of October, though Medtronic has taken over supply reorders in the US (and possibly Canada). Read our J&J 4Q17 report.
- **This roundup estimates Roche's worldwide insulin pump sales at just over $150 million in 2017 (down ~12%).** We estimate that sales totaled ~$39 million (down ~1%) in 3Q17 and $38 million (down ~22%) in 4Q17. Roche's pump revenue for the year reflects minimal contribution from the US, since pump sales stateside were discontinued at the beginning of 2017 and pump supply sales ceased in August. Roche announced on its 4Q17 call, to the surprise of many, that its Solo Patch Pump is to launch in the EU this year - we'll believe it when we see it! Read our Roche 4Q17 report.
- **Valeritas's worldwide V-Go sales were ~$20 million in 2017 (down ~4%).** Sales totaled ~$5 million (up ~4%) in 3Q17 and ~$6 million (up ~20%) in 4Q17. Read our Valeritas 4Q17 report.
- **Cellnovo's worldwide insulin pump sales were ~$1.1 million in 2017 (down ~25%).** Sales totaled ~$220,000 (down ~28%) in 3Q17 and $370,000 (up ~3%) in 4Q17. Read our Cellnovo 4Q17 report.
- **Will 2018 be the start of a resurgence in the pump field?** When 2017 began, Roche and Animas already seemed to be in trouble and there were growing murmurings questioning whether Tandem would pull through a rough patch. We had been describing Insulet as the lone bright spot in the field, and while it continues to drive the largest share of growth, Tandem has recovered and set itself up for very strong product launches this (PLGS) and next year (hybrid closed loop). Meanwhile, Medtronic has overcome sensor manufacturing difficulties and looks ready to drive the 670G at a larger scale.
    - **Will we see new business models in the pump field? Will the current four-year upfront cost model change?** Is automated insulin delivery the field's chance to move the revenue model towards more of a monthly/service-based/subscription approach?

Insulet seems the best positioned to drive this near-term, given the Medicare Part D (pharmacy) designation. Meanwhile, Bigfoot is founded on this very business model, and a WSJ article mentioned that Medtronic is "exploring contracts with insurers" that would link 670G reimbursement to hypoglycemia prevention. Tandem deserves a lot of credit too, as its software update feature has successfully delivered innovation within a four-year warranty. Will we see progress on the business model front in 2018, driven by new deals with payers, software-updateable pumps, and new pharmacy distribution channels?

- **Patch insulin delivery devices designed for type 2 have yet to really take off, though there could be a nice suite of products on the market by the end of 2019.** Valeritas is the only company on the market now, though it has been around $5 million in revenue since 2Q15. Encouragingly, the company intends to make a connected version of the V-Go available by the end of 2018 (via an attachment), and is set to embark on European distribution starting with Italy in the back half of this year. On the fully-featured front, BD's Swatch type 2 patch pump and Insulet/Lilly's U500 Omnipod (both with Bluetooth connectivity) are expected to launch by "September 2019" (BD) and in "2019" (Insulet). Cequr's PAQ and J&J's OneTouch Via patch bolus delivery device have still yet to launch, though the former is CE marked and the latter is cleared by FDA. We haven't heard an update on Cequr in some time, and uncertainty in the future of J&J's diabetes business is preventing the launch of the Via (it is not part of the Platinum Equity deal). Roche's Solo patch pump could also appeal to type 2 diabetes, though we'll have to wait until the launch to see the feature set.
- **Though the 670G is still the only product on the market, 2017 brought the automated insulin delivery landscape more into focus (below), and it's looking like 2019-2020 could bring up to five new hybrid closed loop systems to the US.** Internationally, 2018 could bring two launches (Medtronic 670G and Diabeloop), plus Roche/Senseonics/TypeZero possibly in 2019/2020 after the pivotal wraps up later this year. In the US, Tandem, Bigfoot, Insulet, Beta Bionics, and possibly Lilly could all launch hybrid closed loop systems in the 2019-2020 timeframe. How will these systems stack up in different stakeholders' eyes? What will be the main differentiators - Cost/business model/payer relationships? Form factor? CGM? Algorithm? Add-on decision support/software/apps? Bundles (e.g., Lilly could feasibly bundle insulin with its AID system)? How much of a threat is MDI+CGM+decision support to the AID enterprise? When might we see these systems make their way into type 2?

US AID Pipeline and Timing

Company	Product	Latest Timing	Recent Coverage
Medtronic	MiniMed 670G/Guardian Sensor 3 hybrid closed loop (modulates basal insulin delivery) "Advanced hybrid closed loop" to add automatic correction boluses, including the DreaMed Diabetes algorithm	Available in US, with 20,000+ users as of February 2018 7-13 year old 670G data submitted to the FDA as of February 2018. 2-6 year-old study wrapping up soon. 1,500 patient outcomes RCT has begun randomization. NIH-funded FLAIR trial vs. 670G starting later in 2018, as of ATTD 2018. JPM 2018 suggested launch would occur after April 2019.	Medtronic 4Q17 (February 2018) ATTD 2018 (February) JPM 2018 (January)

Tandem	Basal-IQ: predictive low glucose suspend (PLGS) algorithm integrated into t:slim X2 pump with Dexcom G5 CGM Control-IQ: hybrid closed loop system with Dexcom G6 CGM and TypeZero algorithm integrated into t:slim X2 pump (includes automatic correction boluses) t:sport - hybrid patch pump with integrated Control-IQ algorithm	Submitted to FDA in 1Q18; US launch expected in summer 2018. Pivotal trial results at ATTD 2018. US launch expected in 1H19. Pivotal trial to start in 2Q18, enabling a "rolling" FDA PMA submission in 2H18. Entering trials in 2019; launch expected in the 2020-2021 time frame	Tandem 4Q17 (March) ATTD 2018 (February)
Bigfoot Biomedical	Loop automated insulin delivery service Disposable pump body married to durable controller (no screen or buttons) that talks to next-gen FreeStyle Libre CGM (factory calibrated) and includes a control algorithm. Smartphone to serve as the window to the system and complete user interface. Ypsomed Orbit infusion set to be used in pivotal study.	US pivotal trial expected to start in early 2019 with Abbott's next-gen FreeStyle Libre (IDE Filing by end of 2018). Anticipated "2020" launch. Data from first clinical study (n=20) shared at DTM 2017.	Bigfoot raises additional $18M, closing Series B with $55M; Abbott makes first-time investment! (March 2017)
Insulet	OmniPod Horizon Mode AGC hybrid closed loop algorithm (commercial version of UCSB algorithm); OmniPod with built-in Bluetooth; paired with Dash PDM handheld (locked down Android phone); Dexcom CGM; Ascensia Contour Next BGM.	Five-day hotel study ongoing in pediatrics down to age two years. Depending on the hotel data, Horizon will either move to a pre-pivotal study later in 2018, or do another study before moving ahead. Launch in "probably 2020 timeframe," per JPM 2018.	Insulet 4Q17 (February) ATTD 2018 (February) JPM 2018 (January)
Beta Bionics	Bionic Pancreas iLet 24-hour hybrid or fully closed loop; insulin-only or insulin+glucagon; dual chambered pump with built-	Insulin-only: pivotal trial beginning in April 2019, followed by FDA PMA submission in 4Q19. Bridging	ATTD 2018 (February)

	in algorithm; Dexcom CGM and possibly Senseonics' Eversense; custom dual-cannula infusion set. Cartridges: 1.6 ml insulin cartridge will offer both manual fill and prefilled NovoRapid PumpCart options. Zealand glucagon cartridge will only come in a 1 ml prefilled format (4 mg of glucagon).	study for iLet device expected to begin in May 2018. Bihormonal: pivotal trial beginning in June 2019. FDA submission and launch timing depend on a stable glucagon, among other things. Zealand dasiglucagon feasibility results shared at ATTD 2018; phase 2b study expected to begin in July 2018 using the iLet integrated device.	
Lilly	Pump is "a white disk about the size of a shoe-polish tin" that carries 3-day supply of insulin; Dexcom CGM; Class AP algorithm Pump has an infusion set, and can be worn direct on the body or in the pocket. It will be controlled wirelessly from a handheld and come with a companion app. Pump designed by Deka R&D - firm led by Dean Kamen, Segway inventor	Launch in ~2-3 years, implying ~late 2019-late 2020 from the initial November 2017 announcement. First phase 1 trial began in December 2017 with Dexcom CGM; ClinicalTrials.gov post indicates n=30 study will wrap up by April 2018.	Tidepool partners with Lilly as part of Big Data Donation Project (March) Lilly developing smart pen with insulin titration and AID with its own pump and Dexcom CGM; launch expected in ~2-3 years, trials to start by end of year (November 2017)
WaveForm (AgaMatrix)	Plans to develop a "vertically integrated" AID system with its own CGM, a pump it owns or has built, and a licensed algorithm.	Development to begin in 2018. As of January 2018, WaveForm was finalizing a license of a basic algorithm, which will be modified in the coming months in advance of initial studies. Pump plans TBD.	WaveForm (AgaMatrix) shares CGM details: 14-day wear, no receiver, ~1 cal/day, 11.1%-13.9% MARD in 4 trials; CE Mark in 2018 (January 2018)

International AID Pipeline and Timing

Company / Academic Group	Product	Latest Timing	Recent Coverage

Medtronic	MiniMed 670G/Guardian Sensor 3 hybrid closed loop (modulates basal insulin delivery)	Working to obtain a CE Mark as of February 2018, with launch to follow in select OUS geographies. JPM 2018 expected 670G international launch by April 2019 ("FY18/FY19"), back from the 3Q17 plan to launch by April 2018.	Medtronic 4Q17 (February 2018)
Diabeloop	Diabeloop System Diabeloop algorithm running on a wireless handheld, Cellnovo or Kaleido (ViCentra) patch pump, Dexcom G5 CGM.	Launch expected in 2018 in France, the Netherlands, and Sweden. Diabeloop has submitted its "part" of the hybrid closed loop system for CE Mark (presumably the algorithm). Discussions underway as to which pump is going to come first. Two-arm CE Mark trial ongoing - Cellnovo arm wrapped up, second arm using Kaleido pump.	CES 2018 (January)
Roche (Senseonics & TypeZero)	Roche Accu-Chek Insight pump with Senseonics Eversense XL CGM (180 day implantable) and TypeZero inControl AP algorithm Could it become widely used in DIY systems, per Open Protocol plans?	To be evaluated in NIH-funded iDCL pivotal trial at three EU sites - expected to begin "soon" as of ATTD 2018 (February). Previously expected to complete by late 2018 and support a CE Mark submission. Joined JDRF Open Protocol Initiative as of ATTD 2018.	ATTD 2018 (February) Roche 4Q17 (February) DTM 2017 (November)
Cellnovo	Cellnovo patch pump with integrated TypeZero inControl AP algorithm; presumably a Dexcom CGM Separately used in Diabeloop system (above) and PEPPER project	As of 3Q17, Cellnovo and TypeZero integration was being finalized, with pilot study for validation to follow in a limited number of patients.	Cellnovo receives CE mark for next-gen Bluetooth- and Android-enabled pump (December 2017) Cellnovo 3Q17 (October)
EOFlow	Tubeless patch pump and TypeZero inControl AP Algorithm. No CGM partner announced.	Development to begin in 2018, with regulatory approval expected in early 2019.	EOFlow licenses TypeZero's inControl AP algorithm for patch

	JDRF partnership also funding work to develop single on-body AID patch.	Commercialization expected throughout Asia.	pump (February 2018)
Ypsomed	Closed loop system with YpsoPump (durable pump), CGM (partner not named), and myLife Control smartphone app.	CGM integration expected with YpsoPump in 2018; discussions ongoing with Abbott and Dexcom. Closed loop pivotal trial expected in 2019 with YpsoPump and mylife Control App (allowing for remote bolusing).	Ypsomed rolling out mylife App in 16 EU countries by April 2018 (February 2018) Ypsomed F1H18 (November 2017)
Cambridge	Upcoming long-term studies will use Medtronic's MiniMed 640G/Enlite 3 + Android phone running Cambridge's MPC algorithm.	Commercialization plans unknown. Upcoming long-term studies ranging from three to 24 months, including adolescents (6-18 yrs), young children (1-7 year olds), and newly diagnosed. Upcoming six-month, n=130, Dan 05 study expected to resume in ~May 2018 and wrap up by August 2019 (per ATTD 2018).	ATTD 2018 (February)
Inreda	Bihormonal pump, two CGM sensors for redundancy, fully automated (no meal announcement).	No recent updates. As of October 2016 update on website, preparing for second clinical study and CE Mark received for company's quality system.	Inreda company website update (October 2016) ADA 2016 (June)

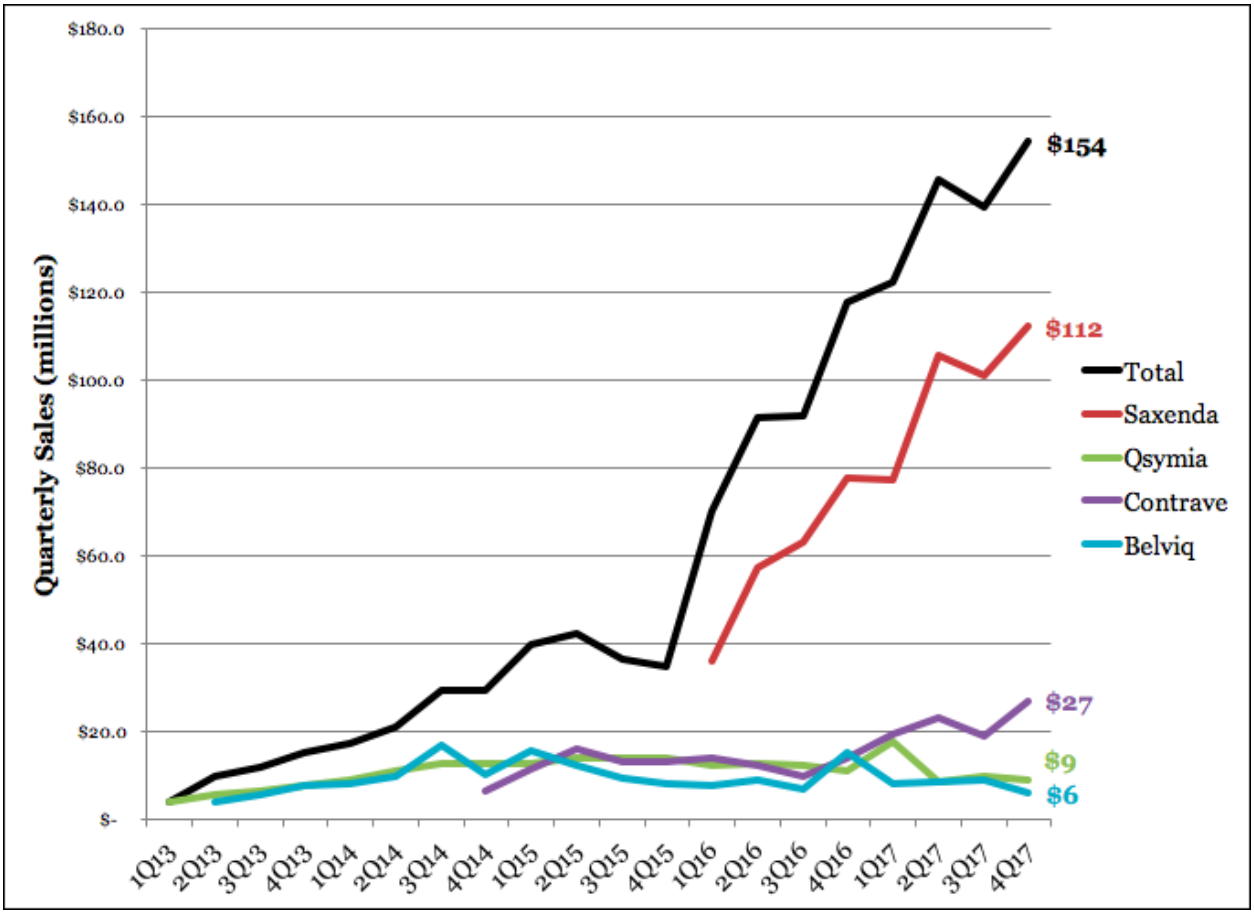
Obesity

Obesity Drug Sales Climb 54% YOY to $559 Million in 2017, Driven by Novo Nordisk's Saxenda (77% Share of Growth); Orexigen Bankruptcy Casts Shadow

- **In 2017, the market for branded obesity drugs grew 54% YOY to $559 million from a base of $364 million in 2016.** While a double-digit YOY jump is notable, it's less impressive when you consider the low base and the fact that growth was driven almost entirely by Novo Nordisk's Saxenda (liraglutide 3.0 mg). Saxenda sales climbed 63% YOY in 2017 to hit $394 million, which is notably more than the market total for 2016. Excluding Saxenda revenue, the market comprised of Orexigen's Contrave, Vivus' Qsymia, and Arena/Eisai's Belviq grew only 27% YOY to $165 million in 2017. By our calculations, Novo Nordisk's high-dose GLP-1 agonist contributed a 77% share of growth for the full year. Pooled sales for the obesity class rose 52% YOY in 3Q17 to $139 million (+31% YOY to $38 million without Saxenda), and grew 38% YOY in 4Q17 to $154 million (+5% YOY to $42 million without Saxenda). While Orexigen's Contrave (naltrexone/

bupropion) was shaping up to be a bright spot, the company filed for bankruptcy earlier this year in disappointing and surprising news, which underscores the steep challenges in this market. Importantly, our pooled analysis is informed by the estimates for Contrave sales that Orexigen provided in its bankruptcy announcement. According to these estimates, Contrave posted $27 million in 4Q17 (nearly doubling YOY) and $88 million in 2017 (+77% YOY). Qsymia sales were only $9 million in 4Q17 (-20% YOY) and $45 million in 2017 (-7% YOY). Belviq revenue came in at $6 million in 4Q17 (-31% YOY) and $32 million in 2017 overall (flat YOY). It's worth noting that Orexigen went bankrupt despite Contrave sales that nearly doubled Qsymia sales and that more than doubled Belviq sales for the 2017 calendar year. By value, Saxenda retained its strong hold on the market, taking home 73% of pooled revenue in both 3Q17 and 4Q17. Behind Saxenda, Contrave captured 14% and 17% of pooled revenue in 3Q17 and 4Q17, respectively, followed by Qsymia at 7% and 6%, then Belviq at 6% and 4%. By volume, market share looks a bit different: Contrave was the #1 prescribed branded weight loss drug in 3Q17, according to Orexigen, so we imagine Saxenda's higher share of sales has to do with its higher list price. We'll be watching with interest in 2018 for any news on Contrave and for clues as to how the Orexigen bankruptcy will impact the obesity drug market. Will Contrave be purchased as an asset and remain available to patients with obesity? One thing is for sure: The obesity market remains seriously stymied by poor reimbursement, underutilization (only ~2% of 600 million people with obesity worldwide receive medical care), stigma against the use of non-lifestyle interventions, weight-based bias from providers and from society, and under-diagnosis of obesity as a disease. The tide is turning ever-so-excruciatingly slowly. We are happy to note increasing industry investment in obesity - most notably, Novo Nordisk will launch the first-ever CVOT in obesity (SELECT) in 2018 to show how a pharmacotherapy (semaglutide) can improve hard outcomes. That said, we'd also love to see much more effort on the prevention front, as science continues to show that obesity is a lifelong disease requiring chronic and intensive management.

Obesity Drug Sales (1Q13-4Q17)



-- by Payal Marathe, Brian Levine, Adam Brown, Ann Carracher, Maeve Serino, and Kelly Close