CLOSER LOOK

MEMORANDUM

## FDA clears Tandem t:slim X2 as first interoperable insulin pump: "alternate controller enabled (ACE) infusion pump" (aka iPump) - February 14, 2019

**Executive Highlights**

- **In highly anticipated news, FDA and Tandem announced today that FDA has cleared Tandem's t:slim X2 as the first interoperable insulin pump - creating a new category called alternate controller enabled (ACE) infusion pumps.** These will be regulated at class II (510(k)) with special controls and are cleared with interoperability in mind -they can be used as part of an automated insulin delivery (AID) system or as a standalone pump (with/without CGM).
- **Following iCGM, this is the second step towards the vision of a plug-and-play, interoperable AID ecosystem with less regulatory burden. The t:slim X2 (and future ACE pumps) will be able to plug into automated insulin delivery systems without the need for an additional clinical trial or PMA submission** - a major win for innovation, speed, and patient choice! For instance, if an AID algorithm is approved to work with Tandem's t:slim X2 ACE pump, and another ACE pump is cleared, the second pump can be integrated into the AID system *without* a new clinical trial or PMA - a clear benefit for interoperable-focused, freedom-of-choice systems like Tidepool Loop. An iController pathway will be the last step needed for the complete plug-and-play vision to be a reality - two out of three components in less than a year is a tremendous step! (Read Tidepool's blog post for more explanation.)
- **The ACE Pump special controls are posted here, and we suspect that most pumps can or will be able to satisfy them. The controls do *not* have accuracy thresholds like iCGM; the focus is on security, reliability of communication, design, and transparency**. The latter is key, similar to iCGM - ACE pumps will have more information on pump performance in the labeling (e.g., pumping accuracy), enabling partners to safely integrate them.
- **Like iCGM, formal company agreements are still needed to share device data and update labeling - i.e., ACE Pumps and iCGMs cannot automatically be used together unless business relationships are in place**. Incorporating a non-ACE pump into an AID system will still require traversing the rigorous PMA process.
- **This exciting clearance brings many questions: How much of an innovation advantage does this bring for Tandem and Dexcom? Will other pump companies pursue an ACE insulin pump indication? Will Tandem choose to integrate with Tidepool Loop?** We think Insulet and Roche, both proponents of interoperability, are likely ACE pump candidates. As the first pump partner for Loop, Insulet seems likely to pursue this designation. Plus, Insulet's Horizon hybrid closed loop is now expected to launch with direct user smartphone control, a logical extension of the "alternate controller enabled" pump indication. Roche seems likely too: it is part of JDRF's open protocol AID initiative, and while it is not in the US pump market now, it does expect to bring its newly launched Solo patch pump to the US. See below for more proposed competitive implications on other companies.

FDA and Tandem announced this afternoon the clearance of Tandem's t:slim X2 with interoperable technology under a new de novo pathway for "alternate controller enabled (ACE) infusion pumps" with special controls.

Colloquially referred to in the field as an "iPump" up until today, an ACE pump is specifically cleared with interoperability in mind. Just like the iCGM category created with Dexcom's G6 last March, ACE pumps are indicated for use with different digitally connected devices (AID controllers, apps, bolus calculators, CGMs, etc.). With this authorization, other pump manufacturers can now cite t:slim X2 as a predicate device and join the ranks as an interoperable ACE pump.

Tandem spearheaded this new regulatory designation, submitting its already-approved t:slim X2 pump as the first interoperable pump to FDA in October. Kudos as well to the FDA for taking yet another step to speed innovation, reduce regulatory burden (while maintaining safety), and foster interoperability!

This continues the drive towards component, plug-and-play interoperability within AID, as we first saw with G6's creation of the iCGM pathway. The goal is to move away from the traditional, system-focused PMA process that can really slow things down and limit iteration and choice. Moving forward, t:slim X2 and all future ACE pumps will be allowed to integrate into AID systems without having to first perform additional clinical trials and submit new PMAs. For instance, if an AID algorithm like Tidepool Loop is approved to work with any iCGM and any ACE pump, future devices with those interoperable indications can be integrated into Tidepool Loop *without* new trials or PMA submissions. Another example is Tandem's next-gen, miniaturized t:sport pump - as long as it meets the ACE pump standards and communicates with the Control-IQ algorithm and iCGM, it will not need a new clinical trial or a PMA submission. Instead, Tandem can get t:sport with Control-IQ cleared under the 510(k) pathway using the t:slim X2 as a predicate device. (The Control-IQ AID controller will be regulated at Class III, separately from the pump.) The benefits should be more component variety and more iteration within both pumps and CGMs, but without triggering the onerous PMA process for traditional AID system changes.

The interoperable designation does *not* mean that elements of an interoperable AID system can automatically be used together; rather, at this stage, the involved organizations must have formal agreements to define product support, complaint reporting, and financial terms. In the future, if a company's communication plan didn't require a formal agreement (i.e., if there were a pump interoperability technical standard), then the components could be more plug-and-play.

The special controls - pasted in the Appendix below - outline the accuracy, reliability, cybersecurity, and clinical relevance requirements for ACE infusion pumps, in addition to the type of studies and data necessary for demonstrating that these standards are met. Several themes that emerged during JDRF/Helmsley's Interoperability meeting were included - regulatory members in the audience, including CDRH's Dr. Courtney Lias, were clearly listening. Dr. Lias told us that ACE pumps are required to have information on pump performance in more resolution than the labeling for typical pumps, enabling partners to better understand the pump's performance - that makes a lot of sense, especially for minimum delivery and dosing accuracy for automated dosing. There is no performance standard for ACE pumps (unlike with iCGM), and we'd guess most current pumps (especially those being developed for AID systems) already do or can meet the controls. The division of ACE vs. non-ACE pumps will come down to who wants to share detailed information, who sees interoperability as an enabler, and how much the ACE pathway carries innovation advantages.

Some of the notable special controls relate to:

- establishing secure interfacing with external devices;
- ensuring safe therapy is maintained when communications with digitally connected controller devices are lost; and
- recording critical events to allow for auditing of communications between digitally connected devices.
- And the definition of an ACE pump: "An alternate controller enabled infusion pump (ACE pump) is a device intended for the infusion of drugs into a patient. The ACE pump may include basal and bolus drug delivery at set or variable rates. ACE pumps are designed to reliably and securely communicate with external devices, such as automated drug dosing systems, to allow drug delivery

commands to be received, executed, and confirmed. ACE pumps are intended to be used both alone and in conjunction with digitally connected medical devices for the purpose of drug delivery."

While both are excellent moves for the field, iCGM seems like a bigger competitive advantage for Dexcom than ACE pump is for Tandem. iCGM has the tough accuracy standard and moved G6 from class III to class II (a tremendous speed advantage); ACE pumps will remain class II and don't have a tough performance moat that competitors will have to cross. We'll see later this year how Tandem and Dexcom use their interoperability designations as the Control-IQ hybrid closed loop is expected to launch this summer. We'll also be eager to see if other pump companies follow.

The existing PMA pathway will stand for the incorporation of non-ACE pumps into AID systems - e.g., if Medtronic wants to update the 670G with new pump hardware, it's a new PMA. AID algorithms will be regulated separated as class III software - e.g., if Tandem creates a Control-IQ 2.0 for the t:slim X2 ACE Pump, it will require a new PMA. We wonder if ACE pumps change the incentives of where to put the AID algorithm - e.g., should the algorithm sit on the ACE pump (like Tandem's Basal-IQ) or on a standalone smartphone app (like Tidepool Loop)? The phrasing "alternate controller enabled" makes us think of an algorithm that sits in a separate, class-III regulated app that talks to the class II pump. Dr. Courtney Lias confirmed with us that the AID algorithm can reside on the ACE pump itself or in a separate app.

Beyond advantages to the manufacturer, as FDA Commissioner Dr. Scott Gottlieb points out in the press release, the ACE pump pathway "has the potential to aid patients who seek more individualized diabetes therapy systems and opens the door for developers of future connected devices to get other safe and effective products to patients more efficiently."

A big question is whether the FDA will create an "iController" pathway for algorithms, which are the critical class III component of AID systems. Tidepool's blog post notes that it is working on the iController pathway with Loop, and we suspect Tandem and Dexcom might try to go this route with Control-IQ (our speculation). See below for more potential competitive implications, as well as our questions and the full special controls.

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## Competitive Implications

**For now, this interoperability is a competitive advantage for Tandem, though it's hard to know how *much* of an advantage it will be.** Unlike the iCGM special controls for accuracy when Dexcom's G6 was cleared, the ACE pump special controls do not have a performance standard or requirement for narrow confidence intervals (i.e., large clinical trial); the numbers in the ACE Pump regulation simply require performance to be *specified* in the labeling. ACE pumps and non-ACE pumps will both be class II, 510(k)-regulated devices. Will other pump companies choose to go this route? We suspect some will, as there are advantages to an ACE insulin pump designation: For Tandem, one immediate benefit is a faster path to getting the miniaturized, screenless, wirelessly controlled durable tubed pump t:sport with the Control-IQ algorithm to market. As long as t:sport meets the ACE pump standards and communicates with Control-IQ and iCGM as expected, Tandem will not need a clinical trial or a PMA to iterate the AID system - it can get t:sport cleared under the 510(k) ACE pump pathway using the t:slim X2 as a predicate device. This expectation has pulled t:sport's expected launch timing to "2H20" instead of the previous "2020-2021." Tandem will also be able to make changes to the pump component of its AID system without requiring a whole new PMA each time - a significant win, especially given Tandem's propensity for iterative innovation.

- **As noted above, it is difficult to ascertain the rigor of the ACE insulin pump special controls and thus the likelihood that other pump companies will be able to quickly follow suit.** The field is moving towards interoperability, and as JDRF's Dr. Aaron Kowalski and Hemlsey's Mr. David Panzirer have commented, there is a distinct competitive advantage to be leveraged. At the JDRF/Helmsley Interoperability meeting, Mr. Panzirer urged the audience: "I'd challenge anyone who thinks that having a closed system is a good idea to rethink that. Ask yourself, is it a competitive advantage or just something leftover? If you ask me, in the future that may come back to bite you." Dr. Kowalski closed the day in a similar tone: "I can virtually guarantee someone will come along with a cheap pump, and they will plop algorithms in, and that's what I'd be thinking about if I were in your shoes." Roche and Insulet are both potential candidates to pursue an ACE pump indication.
    - **Insulet has demonstrated a commitment to interoperability, becoming the first pump partner for Tidepool's Loop.** Moreover, Insulet's Horizon hybrid closed loop is now expected to launch with direct user smartphone control, making it an attractive contender for plug-and-play interoperability. During the company's 3Q18 call, Insulet COO Shacey Petrovic wouldn't directly comment on whether Insulet will submit as an interoperable pump, but noted "The system today, Dash, is designed to be interoperable, and we fully expect to take advantage of all regulatory pathways for Horizon and Tidepool Loop." We expect the decision will come down to the advantages of the new ACE pump special controls. However, given Insulet's commitment to interoperability and plans to be part of Tidepool Loop, we would be surprised if the company did not pursue an ACE pump indication.
    - **Roche was the first to sign JDRF's Open-Protocol Automated Insulin Delivery Systems initiative and just launched its Solo patch pump in pilot markets in the EU.** While plans for Solo-integrated automated insulin delivery have yet to be shared, Roche does expect to bring Solo to the US and intends for the patch pump to eventually be controlled via an app directly on user's smartphones. Given the fierce competition, it would be a strong move for Roche to bring interoperability to the table.
    - **We wouldn't be surprised if others commercializing or developing automated insulin delivery systems - Medtronic, Bigfoot, Lilly, Beta Bionics, etc. - also pursue the ACE infusion pump designation.** Even if they choose to not forge business agreements with other manufacturers allowing the incorporation of their devices into a plug-and-play system, they would still see the clear benefit of not having to perform a new trial for each incorporation into a new system.
- **It will be interesting to see whether the ACE insulin pump category incites other CGM companies to more aggressively pursue the iCGM pathway.** Dexcom is currently the only iCGM on the market and Tandem already integrates with the G6 iCGM via t:slim X2 with Basal-IQ. It would certainly be an attractive option for an iCGM company to integrate its device with the t:slim X2 ACE pump, as neither a clinical trial nor a PMA submission would be necessary (as we understand it). Perhaps this news will encourage Senseonics to pursue an iCGM indication - Senseonics has previously stated an interest in doing so but is currently prioritizing approval of the 180-day Eversense XL and reduced calibration and non-adjunctive dosing claim for the 90-day Eversense. Still, Tandem management was vague at the September Analyst Meeting about integrating other iCGMs with the t:slim X2. In order for devices to be integrated, manufacturers of iCGMs and ACE pumps will still need to establish a business relationship, and the respective devices must be cleared for use with the other category of device (e.g., an ACE pump cleared for use with an iCGM). Given that Dexcom now owns TypeZero, the developer of Tandem's Control-IQ algorithm, this raises the question of whether Tandem would even be able to include another CGM in its system.

- **Will this news encourage Medtronic to move faster into interoperability - either iCGM, ACE pump, or both?** Medtronic's 670G will be leapfrogged on many product features by Tandem's Control-IQ with G6; the pressure will be on to innovate quickly, and obtaining iCGM and iPump status could be a good move. At JPM, Medtronic shared plans to obtain an iCGM and non-adjunctive indication in the April 2019-April 2020 (FY20) window**.**

## Q&A with FDA's Dr. Courtney Lias

**CC: Beyond the two use cases mentioned above - Tandem's follow-on t:sport pump and multiple pumps working with Tidepool Loop - are there other ACE pump use cases?**

**Dr. Lias:** This pump could interact with many types of existing and theoretical digitally connected devices, such as AID controllers, external controllers (e.g., in an app), external bolus calculators (e.g., to inform IOB), decision support tools, CGMs, etc.

**CC: If class III algorithm resides on a class II ACE Pump, are the two just regulated separately now? How does it work if the "external" controller actually resides on the pump?**

**Dr. Lias:** A controller algorithm would be regulated separately from the ACE pump, and the "external device" could be embedded on the pump. This is similar to the bolus calculator case in currently marketed pumps - technically bolus calculators are regulated as a different type of device than the pump they reside on.

**CC: Once an ACE Pump is cleared, can it be integrated with any PMA-regulated CGM without a new PMA submission (provided the companies work together)? In other words, can Tandem integrate with Senseonics Eversense through a label update alone, or is that a new PMA submission because Eversense is not an iCGM?**

**Dr. Lias:** An ACE pump could be used with other, legally marketed devices that are cleared or approved to be used with an ACE pump (e.g., if a sensor was approved to integrate with ACE pumps as a display). The ACE pump regulation is agnostic to the regulatory pathway of the digitally connected device.

**Q: Any reason why you went with "ACE pump" instead of "iPump?"**

**Dr. Lias:** The concept of pumps designed to be compatible with alternate controllers is an important regulatory distinction between ACE pumps; class III sensor-augmented pumps; and class II insulin pumps. So the name became "alternate controller enabled," and it is also pronounceable, as a bonus.

## Close Concerns' Questions

**Q: How large are the innovation and speed advantages of the ACE Pump indication? Beyond the t:sport and Tidepool Loop cases noted above,** what are the other use cases where an ACE pump indication simplifies things? How will Tandem and Dexcom capitalize on their first-in-class ACE pump and iCGM indications this year?

**Q: Are ACE pumps afforded more leniency on regulation around design changes?**

**Q: Which manufacturers will follow as the next ACE pumps to receive clearance?**

**Q: How rigorous are the ACE pump special control? How are they measured?** How much work will they require existing pump companies to submit? Dr. Lias will discuss some of this at ATTD.

**Q: If a class III control algorithm is integrated into the ACE pump, are there still advantages to this pathway? Or is the class III algorithm regulated as separate from the ACE pump, even if the algorithm resides *on the pump*?**

**Q: Will companies move controllers towards separate standalone smartphone apps, rather than integrated into the pump? (e.g., Tidepool Loop)** For now, most companies - Tandem, Bigfoot, Insulet, Lilly - have said they plan to put the control algorithm into the pump, but enable the app to serve as a user interface and location for remote bolusing. This brings a nice experience advantage, since the user will remain in closed loop even when the phone is out of range.

**Q: Will we see an iController regulatory pathway?**

**Q: As we move closer toward component systems of interoperable parts, how are companies planning to handle liability, financials, and customer service? Will the pump, CGM, or algorithm maker be responsible for troubleshooting?**

**Q: What other types of insulin delivery devices can fall under the category of "ACE infusion pump", if any?**

## Appendix: ACE Insulin Pump Special Controls

**Pasted from [FDA's website]:**

1. Design verification and validation must include the following:

a. Evidence demonstrating that device infusion delivery accuracy conforms to defined user needs and intended uses and is validated to support safe use under actual use conditions.

i. Design input requirements must include delivery accuracy specifications under reasonably foreseeable use conditions, including ambient temperature changes, pressure changes (e.g., head- height, backpressure, atmospheric), and, as appropriate, different drug fluidic properties.

ii. Test results must demonstrate that the device meets the design input requirements for delivery accuracy under use conditions for the programmable range of delivery rates and volumes. Testing shall be conducted with a statistically valid number of devices to account for variation between devices.

b. Validation testing results demonstrating the ability of the pump to detect relevant hazards associated with drug delivery and the route of administration (e.g., occlusions, air in line, etc.) within a clinically relevant timeframe across the range of programmable drug delivery rates and volumes. Hazard detection must be appropriate for the intended use of the device and testing must validate appropriate performance under the conditions of use for the device.

c. Validation testing results demonstrating compatibility with drugs which may be used with the pump based on its labeling. Testing must include assessment of drug stability under reasonably foreseeable use conditions which may affect drug stability (e.g., temperature, light exposure, or other factors as needed).

d. The device parts that directly or indirectly contact the patient must be demonstrated to be biocompatible. This shall include chemical and particulate characterization on the final, finished, fluid contacting device components demonstrating that risk of harm from device-related residues is reasonably low.

e. Evidence verifying and validating that the device is reliable over the ACE pump use life, as specified in the design file, in terms of all device functions and in terms of pump performance.

f. The device must be designed and tested for electrical safety, electromagnetic compatibility, and radio frequency wireless safety and availability consistent with patient safety requirements in the intended use environment.

g. For any device that is capable of delivering more than one drug, the risk of cross-channeling drugs must be adequately mitigated.

h. For any devices intended for multiple patient use, testing must demonstrate validation of reprocessing procedures and include verification that the device meets all functional and performance requirements after reprocessing.

2. Design verification and validation activities must include appropriate design inputs and design outputs that are essential for the proper functioning of the device that have been documented and include the following:

a. Risk control measures shall be implemented to address device system hazards and the design decisions related to how the risk control measures impact essential performance shall be documented.

b. A traceability analysis demonstrating that all hazards are adequately controlled and that all controls have been validated in the final device design.

3. The device shall include validated interface specifications for digitally connected devices. These interface specifications shall, at a minimum, provide for the following:

a. Secure authentication (pairing) to external devices.

b. Secure, accurate, and reliable means of data transmission between the pump and connected devices.

c. Sharing of necessary state information between the pump and any digitally connected alternate controllers (e.g., battery level, reservoir level, pump status, error conditions).

d. Ensuring that the pump continues to operate safely when data is received in a manner outside the bounds of the parameters specified.

e. A detailed process and procedure for sharing the pump interface specification with digitally connected devices and for validating the correct implementation of that protocol.

4. The device must include appropriate measures to ensure that safe therapy is maintained when communications with digitally connected alternate controller devices is interrupted, lost, or re-established after an interruption (e.g., reverting to a pre-programmed safe drug delivery rate). Validation testing results must demonstrate that critical events that occur during a loss of communications (e.g., commands, device malfunctions, occlusions, etc.) are handled appropriately during and after the interruption.

5. The device design must ensure that a record of critical events is stored and accessible for an adequate period to allow for auditing of communications between digitally connected devices, and to facilitate the sharing of pertinent information with the responsible parties for those connected devices. Critical events to be stored by the system must, at a minimum, include:

a. A record of all drug delivery

b. Commands issued to the pump and pump confirmations

c. Device malfunctions

d. Alarms and alerts and associated acknowledgements

e. Connectivity events (e.g., establishment or loss of communications)

6. Design verification and validation must include results obtained through a human factors study that demonstrates that an intended user can safely use the device for its intended use.

7. Device labeling must include the following:

   a. A prominent statement identifying the drugs that are compatible with the device, including the identity and concentration of those drugs as appropriate.

   b. A description of the minimum and maximum basal rates, minimum and maximum bolus volumes, and the increment size for basal and bolus delivery, or other similarly applicable information about drug delivery parameters.

   c. A description of the pump accuracy at minimum, intermediate, and maximum bolus delivery volumes and the method(s) used to establish bolus delivery accuracy. For each bolus volume, pump accuracy shall be described in terms of the number of bolus doses measured to be within a given range as compared to the commanded volume. An acceptable accuracy description (depending on the drug delivered and bolus volume) may be provided as follows for each bolus volume tested, as applicable: number of bolus doses with volume that is <25%, 25% to <75%, 75% to <95%, 95% to <105%, 105% to <125%, 125% to <175%, 175 to 250%, and >250% of the commanded amount.

   d. A description of the pump accuracy at minimum, intermediate, and maximum basal delivery rates and the method(s) used to establish basal delivery accuracy. For each basal rate, pump accuracy

shall be described in terms of the amount of drug delivered after the basal delivery was first commanded, without a warm-up period, up to various time points. The information provided must include typical pump performance, as well as worst-case pump performance observed during testing in terms of both over-delivery and under-delivery. An acceptable accuracy description (depending on the drug delivered) may be provided as follows, as applicable:

i. The total volume delivered 1 hour, 6 hours, and 12 hours after starting delivery for a typical pump tested, as well as for the pump that delivered the least and the pump that delivered the most at each time point.

e. A description of delivery hazard alarm performance, as applicable. For occlusion alarms, performance shall be reported at minimum, intermediate, and maximum delivery rates and volumes. This description must include the specification for the longest time period that may elapse before an occlusion alarm is triggered under each delivery condition, as well as the typical results observed during performance testing of the pumps.

f. For wireless connection enabled devices, a description of the wireless quality of service required for proper use of the device.

g. For any infusion pumps intended for multiple patient reuse, instructions for safely reprocessing the device between uses.

*-- by Maeve Serino, Brian Levine, Adam Brown, and Kelly Close*