Open Source Automated Insulin Delivery

Downey, Laura; Quigley, Muireann; O'Donnell, Shane; Melvin, Tom

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Open Source Automated Insulin Delivery: Potential Pathways to Regulatory Approval

BASED ON RESEARCH BY

DR LAURA DOWNEY
PROF MUIREANN QUIGLEY
DR SHANE O' DONNELL
DR TOM MELVIN

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Background

Open-source automated insulin delivery (OS AID) systems have been developed by and for people with diabetes to better manage their condition. They are comprised of open-source, user-built apps installed on a smartphone or small computer which, when paired with an insulin pump and a continuous glucose monitor, (semi-)automate the process of insulin delivery. As user-led initiatives, the apps have been developed outside the usual manufacturing environments. Until recently none had gained (or had applied for) regulatory clearance or approval in any jurisdiction.

However, in early 2023, using one of the open-source algorithms developed by the diabetes community as the basis for a mobile app, the non-profit Tidepool successfully gained regulatory clearance from the US Food and Drug Administration (FDA). This note is based on research we undertook regarding this milestone,

Since the process for gaining regulatory approval can be complex and opaque for those unfamiliar with medical devices regulation, this note provides a broad overview of the regulatory pathways and processes that may be encountered by those seeking regulatory approvals for OS AID apps/software in the United States (US), the European Union (EU - including Northern Ireland), or Great Britain (GB). It focuses on the distinctions in institutional structure, device classification, and processes for regulatory approval or conformity assessment in the three jurisdictions.

United States

The principal legislation is the Federal Food, Drug, and Cosmetic Act. Applications for market approval are (mostly) handled centrally by the FDA.

Device Classification

The US has 3 device classifications:

- Class I - lowest risk
- Class II - medium risk
- Class III - highest risk

Generally, devices are classified based on their novelty. Where similar devices exist, a new device will most likely follow the same categorisation. If a device is completely novel with no existing similar device, it will likely be treated as Class III devices.

Regulatory Process

Class I devices mostly self-declare conformity and are subject to light touch regulation.

Class II devices go through the 510(k) process if there is an existing predicate device with which they are 'substantially equivalent'. A device is substantially equivalent if it has the same intended use as the 'predicate device' – the device on which a claim of equivalence is based – and either:

- Has the same technological characteristics as the predicate device; or
- It can be shown to be just as safe and effective as the predicate device and raises no further distinct questions of safety and efficacy.

Where there is no existing predicate device, devices are normally automatically Class III and are required to undergo the premarket approval process which includes providing clinical studies.

However, the De Novo process can be used by manufacturers of devices where no predicate exists where they believe they are less risky than a Class III device. This process will result in a risk classification being assigned to the device which can then itself be relied upon by future devices as part of the 510(k) pathway.

The De Novo process can also result in new 'special controls' being added. These are conditions that subsequent 510(k) applications must meet and may include the need for clinical studies to be provided.

This means that

Tidepool Loop relied on an existing predicate device to go through the 510(k) pathway. As part of the De Novo process for the predicate device 'special controls' were required. This meant that Tidepool Loop needed to provide clinical evidence of the devices safety and clinical efficacy. Applications for other OS AID algorithms will need to follow the same process and special controls.

European Union

The applicable EU legislation, for devices which are not in-vitro diagnostic devices, is Regulation (EU) 2017/745 on Medical Devices (EU MDR 2017). Devices in certain risk classes must undergo a conformity assessment to ensure they are safe and perform as intended. These are handled by decentralised private third parties called Notified Bodies.

Post-Brexit there is a dual system of regulation in the UK and, as such, Northern Ireland continues to be subject to EU medical devices' rules.

Device Classification

The EU has 4 device classifications:

- Class I – lowest risk
- Class II
- Class IIb
- Class III – highest risk

Classification is based on a cascading rule system set out in Annex VIII of the EU MDR. Either Rule 11 or 22 are likely to apply to Tidepool Loop and other OS AID apps.

Rule 11 applies to "[s]oftware intended to provide information which is used to take decisions with diagnosis or therapeutic purposes." Where there is a risk of "serious deterioration of a person's state of health" then the device is Class IIb. Where there is a risk of "death or an irreversible deterioration of a person's state of health", then it is deemed a Class III device.

Rule 22 states that "active therapeutic devices with an integrated or incorporated diagnostic function which significantly determines the patient management by the device" are Class III devices.

Regulatory Process

Class I devices can mostly self-declare conformity. Some Class I and IIa devices will require conformity assessment. Class IIb and III devices are subject to more rigorous assessment with Class III devices receiving the most scrutiny.

All devices applying for conformity assessment must have a clinical evaluation. Manufacturers of devices can rely on data from existing devices in their application where the applicant device is deemed to be equivalent to that existing device.

To demonstrate equivalence devices must meet certain biological, technical, and clinical criteria. High risk devices will also require a contract with the equivalent device's manufacturer allowing access to the full technical documentation of the equivalent device.

Two potential comparator products - Diabeloop and CamAPS FX - gained regulatory approval in the EU in 2018 and 2020 respectively. However, they were conformity assessed under the older MDD rules and continue to be marketed under so-called legacy certification. As such, once this expires, they will themselves will be required to meet the more stringent requirements of the EU MDR.

This means that

As there may be a risk of death if the wrong insulin does is calculated, if Rule 11 applies, it is probable that Tidepool Loop and other OS AID apps would be deemed Class III devices. Equally, if Rule 22 applies, they would also be deemed to be Class III devices.

Although the equivalency route has in the past been an attractive one in the EU, given the new requirements and the need for a contract with the equivalent device manufacturer, pursuing conformity through the standard pathway may be more feasible for Tidepool Loop and other OS AID apps.

Great Britain

The applicable legislation here are the Medical Devices Regulations 2002 (SI 2002/618 as amended).* These Regulations derive from older EU law: Directive 90/385/EEC concerning active implantable medical devices (AIMDD) and Directive 93/42/EEC concerning medical devices (MDD) and Directive 98/79/EC on in vitro diagnostic medical devices (IVDD).

Decentralised UK Approved Bodies (previously Notified Bodies under EU law) handle applications for conformity whilst guidance is provided by the Medicines and Healthcare products Regulatory Agency (MHRA).

Device Classication

Classification rules in Annex IX of the MDD apply. Software is treated as an active device and so Rule 9 is the probable applicable rule.

*Note that the Medicines and Medical Devices Act 2021 is the primary legislation governing medical devices in the UK. However, it mainly contains delegated powers to enable new regulations to be implemented and existing ones to be amended.

This states that "[a]ll active devices intended to control or monitor the performance of active therapeutic devices in Class IIb, or intended directly to influence the performance of such devices are in Class IIb."

As per Rule 11, insulin pumps are Class IIb device because they administer a "potentially hazardous medicine". This means that, because an OS AID app in controls the insulin pump, as per Rule 9, it would also be Class IIb. However, as we discuss in the next section, these classification rules may be set to be tightened in future regulations.

Regulatory Process

Medical devices in GB follow similar rules and conformity assessment procedures to those in the EU with some differences. The main differences in relation to device equivalency requirements is that the evidentiary requirements are not as strict as those under the EU MDR and no contract with the manufacturer of the claimed equivalent device is required.

Recent Government proposals suggest that equivalency requirements in GB will change in the future. They have suggested that requirement will be tightened so that 'entire equivalency' will need to be shown. However, it is as yet unclear as to what this means.

This means that

Tidepool loop and other OS AIDs will mostly likely be Class IIb devices under current rules. Whilst, for the time being, it may be easier to submit evidence and rely on data of equivalent devices in GB than in the EU, this situation is likely to change in the near future given the recent proposals for regulatory change in the UK.

This note is based on research presented in Laura Downey, Shane O'Donnell, Tom Melvin, and Muireann Quigley, "A European regulatory pathway for Tidepool loop following clearance in the United States?" *Diabetic Medicine* 2023;00:e15246. https://doi.org/10.1111/dme.15246

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