US Food and Drug Administration's Approval of Aripiprazole Tablets With Sensor: Our Perspective

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The US Food and Drug Administration (FDA)'s recent approval of aripiprazole tablets with sensor (Abilify MyCite, Otsuka) was met with a myriad of reactions from the media and the public.[1,2] Recent publications expressed a wide range of concerns regarding the product, such as its potential to infringe on patient privacy and autonomy, create an adversarial dynamic between clinician and patient, be used in medicolegal situations, or affect insurance coverage.[1,2] We agree that these are important issues requiring a broad discussion. However, discussion of these issues to date has largely been obscured by sensationalism, exemplified by publication titles such as "Swallowing a Spy—The Potential Uses of Digital Adherence Monitoring"[1] and "First Digital Pill Approved to Worries About Biomedical 'Big Brother.'"[2] We hope that this piece facilitates a more rational and measured dialogue surrounding the product's actual capabilities, FDA's decision to approve the product, and any ethical concerns raised by the product.

Our review of the drug, the chip inside the drug, the patch worn by the patient, the mobile application intended for use by patients, and the web portal intended for use by clinicians and caregivers was informed primarily by the results of several human factors studies assessing whether patients with schizophrenia, bipolar I disorder, and major depressive disorder (the approved indications for aripiprazole tablets) could use the product as intended, in addition to the safety evaluation of adding the device to the drug. In these human factors studies, tasks (such as ability to correctly utilize the different parts of the system) were considered "critical" if failure to perform that task properly had the potential to interfere with prescribed aripiprazole use. The error rate on such tasks was evaluated over the course of product development and served as an indicator to guide modifications for improvement in usability. The device components were reviewed separately, prior to the review of the overall drug-device combination. Aripiprazole tablets were approved in 2002, and the efficacy of aripiprazole for schizophrenia, bipolar disorder, and adjunctive treatment of major depressive disorder did not need to be reestablished.

As a regulatory agency, our main findings from this experience are that simplicity is critical for products that integrate a drug with technology and that human factors studies are essential. Some ancillary features that we initially thought would be useful instead caused problems, resulting in the potential for medication error, which was inadvertently increased by features that did not work as intended. In addition, unexpected patient misinterpretation of product instructions also caused errors in proper use of the product. For example, attempts to incorporate a reminder function into the app inadvertently increased the risk of overdose in cases in which detection of product ingestion was delayed. We also observed that a common cause of error in the human factors studies was the tendency for some patients to interpret instruction statements literally. The phrase "Use the product as you would do at home" was especially problematic because some participants ingested the tablet without using all of the device components of the MyCite system, reasoning that "I only take a pill at home; I don't wear a patch or use my phone when I take my medication."

Lost in the media discussion of MyCite are the concerns shared by the FDA and Otsuka about the potential ethical issues of monitoring drug ingestion, as well as the close collaboration between FDA and Otsuka during product development to address these concerns. For example, incorporation of the requirement that patients must actively choose whether to share their information with clinicians and caregivers came directly from a committee of bioethicists consulted by Otsuka to protect patient privacy. Individuals concerned with patient privacy violations also appear to be unaware that data compiled by Otsuka through patient use of the app must be compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), specifically HIPAA laws and regulations regarding disclosure of protected medical information; these were considered and addressed early in the development process.

Several additional concerns[1,2] expressed about the product stem from inaccurate assumptions made about the product's capabilities. The Bluetooth signal sent from the chip to the patch is encrypted and sent only between the paired devices. Other Bluetooth devices cannot receive or

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intercept the signal. The patch is not outfitted with a GPS transmitter, cannot connect directly to the internet, and has no means of capturing audio or video. The product cannot be used to track the user's whereabouts, perform surveillance of the user or individuals near the user, or function as a "spy" or an extension of "Big Brother" as has been suggested.[1,2]

In summary, there is no evidence that this product infringes on patient autonomy. In fact, there are several parts to the system that must be integrated to work, any one of which, if intentionally left out, would thwart the MyCite system: failing to take the pill, taking the pill without using the additional device components, failing to wear the patch properly, failing to install or configure the app, failing to sync the app, and deciding not to share health data with clinicians or caregivers.

No data were collected during the product's development suggesting that the product impacts adherence or influences patient behavior. The FDA's conclusion is simply that the pill, patch, and app function as intended and that most patients with schizophrenia, bipolar I disorder, and major depressive disorder could successfully use the product as demonstrated in the most recent human factors study.

FDA shares the concerns raised by the public regarding potential product use in medicolegal situations and potential use by insurance companies in decisions to pay for care. Although it is outside of FDA's regulatory and enforcement mandate, a national discussion could help determine if more efforts are needed to protect patient data from digital medicines and applications. Our hope is that the necessary discussion rests on rational facts rather than emotional reactions to this new technology.

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