Ensuring public trust in digital therapeutics: a pharmacopeial perspective

Michael Ambrose, PhD

For over 200 years, the United States Pharmacopeia (USP), an independent, nonprofit, scientific organization, has adapted to deliver on our mission to help ensure the quality of medicines globally, including emerging modalities. From recipe-based preparations to small molecules to complex biologicals, USP accomplishes its mission by setting public standards in collaboration with industry, academia, regulators, and practitioners. USP publishes these standards in the official *United States Pharmacopeia-National Formulary* (USP-NF), as well as providing the required physical reference standards. These standards, recognized in over 140 countries, strengthen trust in medicines for pharmacists and other health care providers, regulators, payers, and of course, patients.

But how does quality and trust apply when the medicine is a software or digital-only format? Digital therapeutics (DTx), an emerging modality, offers the potential to help patients prevent, manage, and treat physical, mental, and behavioral conditions. The health care provider (HCP) recommending or prescribing the DTx trusts that it will deliver the intended result, while the patient trusts that it will treat their condition. This is even more relevant if the DTx is recommended or prescribed in lieu of traditional therapy. USP, collaborating with stakeholders, is working to facilitate discussions on how quality attributes can be ensured in this critical emerging modality.

Here, we will define DTx as a therapeutic modality that has either a software-based component or digital-only format that manages or treats a medical disorder and can be used in conjunction with or in lieu of traditional therapeutics. The modality should offer evidence-based support for claims of safety and efficacy.

Faced with the COVID-19 pandemic and the subsequent social disruptions, many people are experiencing increased stress and other mental health conditions. The U.S. Food and Drug Administration (FDA) issued guidance to help “increase access to digital therapeutics while individuals are following ‘stay at home’ orders or practicing social distancing.” The guidance states that “FDA does not intend to object to the distribution and use of [certain] computerized behavioral therapy devices and other digital health therapeutic devices for psychiatric disorders” that are not in compliance with certain regulatory requirements, “where such devices do not create an undue risk in light of the public health emergency.”¹ However, there are no guidelines for those products released once the guidance is no longer in effect.

The guidance provides potential impetus for innovation, but also potential risk for products of inferior quality or products not capable of meeting the needs of the patient. At the 2019 DTx East conference in Boston, Randall Kay, CMO of Click Therapeutics, stated, “As we develop and grow and have new interventions I don’t think we should go to the

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assumption that risk is low....I think we should go with the assumption that risk might be there, and we have to find it.”² This stands true today, driving greater need to ensure the quality of new modalities. Therefore, quality standards are important and as vital today as they have been for medicines for hundreds of years.

The increased interest in digital health is evidenced by the investments in the industry. Rock Health recently reported that for the first half of 2020, investments in digital health reached \$5.4 billion. This is on track to exceed funding of 2019 of \$7.4 billion, of which the behavioral applications funding is \$588 million.³ We must recognize that some of those entering this space may have experience in software but not patient and health outcomes, the critical therapeutic nature of a DTx.

For this perspective, in conjunction with the recently published USP white paper “The Role of Public Standards in Assuring Quality of Digital Therapeutics” (www.usp.org/dtx), we propose that the pharmacopeial approach can evolve to meet the quality assurance needs of the DTx industry, as well as support continued innovation in this emerging modality. Here, we pose 2 questions:

- Can the value of public standards extend to DTx?
- Can the pharmacopeial approach be applied to DTx?

Quality standards: the foundation for accelerated innovation. Standards provide the benchmark of quality, allowing the industry to concentrate on innovation. Standards reduce the barrier to entry and risk of innovation. Heyward et al. (2018) published a review of the value of public standards with emphasis on USP standards.⁴

Standards reduce regulatory uncertainty. Standards provide the capability to assess quality uniformly across all submissions, establishing the foundation that must be met for consistent and timely review. The FDA Center for Devices and Radiological Health (CDRH) recently provided its perspective that quality standards may reduce the time required for premarket review by providing an approach to reduce one-off evaluations and requests for additional information.⁵

But can quality standards drive the adoption of DTx? In the Viewpoints article by Coder and Parcher (also in this issue), they recommend industry standards to which DTx must adhere.⁶ However, these standards address the therapeutic nature, not the product itself. USP, an internationally recognized standard-setting organization, provides the tools for evaluation of product quality. These tools allow industry and regulators to test the quality of the product.

Understanding that DTx are software-based, one must consider the consequences of poor quality. In reviewing the CDRH database containing Medical Device Recalls,⁷ the number one cause of recalls is software related. Between 2002 and 2020, over 500 recalls for software failures included (a) failure to determine correct analyte levels; (b) failure to calculate required dose; (c) failure to calibrate correctly; (d) upgrades/revisions not approved or cleared before release; and (e) security gaps that potentially can release personal data.

There are more than 80 software standards used by CDRH. These standards address aspects of the quality management systems that document the process. However, do they address the uniqueness of DTx—that they treat people?

In addressing this need for quality standards and to collaborate with the DTx community, USP and the Digital Therapeutic Alliance (DTA) held a roundtable in 2018. With

over 40 DTA members, the discussions focused on the pharmacopeial approach as the starting point. From those discussions, USP published the previously mentioned white paper (www.usp.org/dtx).

In this paper, we ask what quality is and how do we instill public trust. We introduce 3 concepts of a finished DTx:

Concept 1: A DTx product is composed of basic ingredients similar to traditional therapeutics.

Concept 2: The digital active pharmaceutical ingredient (dAPI) is the algorithm that is the therapeutic basis of the product.

Concept 3: The code that enables the dAPI to provide its therapeutic effect is the digital excipient ingredient.

The dAPI, inherent to the product and created by the developer, undergoes review and quality assessment. However, the digital excipient may not be fully written by the developer. This code, if obtained from third parties, may not be as quality controlled as the dAPI. In fact, it may even be “software of unknown provenance.”

From these concepts, we define 4 attributes that are foundational to compendial quality. These attributes are not necessarily the only quality attributes, but they serve as thought starters for further discussion.

Identity: What distinguishes one DTx (or ingredient) from a similar DTx (or ingredient)? In chemical medicines, this is the chemical structure. In biological medicines, it may be a functional assay. For DTx, with its rapid revisions, absolute code identity is not advisable. Can identity be the expected behavior or other characteristics of the functional code?

Strength: How “much” dAPI is present? For DTx, is strength how often the patient is exposed to the DTx? Is this the differential parameter configuration or speed of completing a level (in a multilevel DTx experience)?

Purity: The amount of the expected ingredient in the product. For DTx, the presence of errors (bugs, malware) may degrade performance or illicit undesirable behavior. It may also result in data and security leaks.

Performance: Can the drug product deliver the expected therapeutic outcome. For DTx, is this the reaction time of the algorithm or refresh rate of the graphics?

Other areas include safeguarding personal information. These may even be considered a safety aspect of the DTx and include the following:

- Safeguarding of privacy/confidentiality
- Data security
- Integration/usability
- Data rights/ownership

QUALITY DTX NEEDS YOU

As DTX therapies continue to be developed, quality is critical to the evolving nature of health care. Public trust is imperative to sustain and promote patient adherence and usage. To achieve this trust, from the HCP who recommends and prescribes, to the patient who trusts and adheres to the therapy, to the payers that provide reimbursements, they all rely on the DTX to provide expected medical outcomes. This becomes more important with outcome-based reimbursements and inclusion into managed care formularies.

Although not directly involved in these aspects, USP, in concert with stakeholders, creates and publishes standards that help ensure quality and instill trust in medicines. As health care and technology increasingly intersect, USP is collaborating with stakeholders to further shape what quality means for the DTX.

Please read our white paper “The Role of Public Standards in Assuring Quality of Digital Therapeutics” (www.usp.org/dtx) and share your input on 2 key questions that the paper raises by emailing us your thoughts (DTXwhitepaper@usp.org).

- Can the value of public standards extend to DTX?
- Can the pharmacopeial approach be applied to DTX?

We look forward to collaborating with you on the future of medicine.

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