The role of public standards in assuring quality of digital therapeutics

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Digital therapeutics

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“The value of a pharmacopeia depends on the fidelity with which it conforms to the best state of medical knowledge of the day … Usefulness depends upon the sanction it receives from the medical community and the public, and the extent to which it governs the language and practice of those for whose use it is intended.”

Jacob Bigelow, 1808

“For nearly two centuries, USP has helped develop public standards to help people in the US and around the world trust the quality of their medicines. Consistent with 200 years of supporting innovation, USP is proud to bring forward new thinking to define quality attributes of digital therapeutics and facilitate its widespread adoption while ensuring quality in this evolving medicine modality.”

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Abstract

For nearly 200 years, the pharmacopeial approach has served to establish a common foundation upon which the quality of medicines can be evaluated, thereby building trust in the healthcare system and enabling innovation to thrive. The approach has evolved over the years to address new types of medicines (i.e., from chemical medicines to biologics) and incorporate new, more rigorous evaluation methodologies (i.e., from qualitative recipes to quantitative quality assessments). U.S. Pharmacopeia (USP) continues to build upon this foundation by exploring the applicability of our quality framework to emerging technologies.

An area of increasing acceptance and promise is digital health and, more specifically, digital therapeutics (DTx). In just the area of DTx, there is a broad range of potential applications for the advancement of healthcare and the quality requirements specific to them. For this paper, we propose that the pharmacopeial approach can further evolve to meet the quality assurance needs of a very specific emerging class of digital therapeutics driven by high-quality software programs to prevent, manage, or treat a spectrum of medical conditions. In exploring this approach, we propose the following set of key questions, and we welcome comments and open discussion on the proposed concepts:

- Can the value of public standards be extended to DTx products?
  - How are DTx different from and similar to other types of therapies?
  - What are the needs and gaps in the quality assessment of DTx?
  - What is the potential impact of poor-quality DTx products to the patients?
- How can the pharmacopeial approach to determining and assessing the critical quality attributes of a medicine be applied to DTx?
  - How might the concepts of active ingredients and excipients be applied to DTx?
  - What contributions could general chapters and monographs have in the context of DTx?
  - How can the critical quality attributes of a DTx be defined (e.g., concepts such as identity, strength, purity, and performance)?
  - How might these critical quality attributes for DTx be assessed?
  - How can standards prevent or identify substandard or falsified DTx?

Introduction

USP is a nongovernment, nonprofit scientific organization founded in 1820 with the objective of bringing quality uniformity to medicines in the United States. Congress recognized the *United States Pharmacopeia–National Formulary (USP–NF)* as an official compendium of the United States as stated in the Federal Food, Drug, and Cosmetic Act of 1938[1] (FD&C Act), which makes the standards enforceable by the U.S. Food and Drug Administration (FDA). Today, the USP continues this mission through a science-based and public process for the development of official Documentary Standards and physical Reference Standards. This is a well-established process that works in concert with industry, academia, the FDA, other regulatory authorities, and other stakeholders to assure the quality of medicines and bolster the public's trust in them. USP sets public standards for the identity, strength, purity, and performance of medicines. It is important to reiterate that USP does not set these standards on its own but in collaboration with relevant stakeholders. Through public forums, workshops, summits, and other appropriate venues, USP provides a platform for open discussion and deliberations with respect to the formation and setting of standards, both documentary and physical, for all to abide. USP's capability of convening such a wide range of stakeholders with the common goal of creating public standards ensures an active voice to the respective industries and regulatory agencies and promotes the relevance and value of those standards.

While USP's mission of assuring quality medicines remains the same, the standards themselves have significantly evolved in lockstep with the advancement of medicines and therapies. USP standards initially focused on drugs that tended to be simpler in molecular structure (i.e., small molecules), but as the industry evolved, they have expanded to also include more complex drugs such as biologics. At the same time, USP's quality standards have also evolved from qualitative assessments to providing specific guidance using appropriate scientific analytical methods.

In addition to medicines, USP has also had a historic role in assuring the quality of medical devices, as detailed in the 1990 book, *The Medical Device Industry: Science, Technology and Regulation in a Competitive Environment*. Early USP medical device standards (circa 1900) included cotton as an absorbent, reagents used in diagnostic tests, and sterilization for surgical dressings, glass, and metal utensils. This led to a role for USP in medical device standardization set forth in the 1976 Medical Device Amendments.[2] Currently, the FDA

includes in its Recognized Consensus Standards Database nearly two dozen USP standards in biocompatibility, sterility, and general plastic surgery/general hospital areas as relevant to medical devices.[3]

Current Standards

The Federal Food, Drug, and Cosmetic Act (FD&C Act) recognized the *United States Pharmacopeia* as an "official compendium" and defined the term "drug" as an article recognized in it. No such recognition was extended in the definition for devices until the 1976 Medical Device Amendments. Although these amendments recognized articles in the *USP–NF* as devices, the recognition is limited to misbranding only. Section 502(e) of the FD&C Act requires a device to bear its established name as contained in the *USP–NF* in the absence of any designation by the FDA. Section 508 of the FD&C Act requires that two or more names may not be applied to a single device or to two or more devices that are substantially equivalent in design and purpose.

There is no doubt that we have entered an exciting era in which therapies are increasingly innovative and complex. New forms of medicines such as combination products, theranostics, and digital medicines are blurring the traditional line between drugs and devices as well as in the manner in which they deliver therapeutic effects. These include the use of Software as a Medical Device (SaMD) and Software in a Medical Device (SiMD) such as in a continuous glucose monitor.

This raises the key issue of how to assess quality for these new therapies. The International Medical Device Regulators Forum (IMDRF), a voluntary group of medical device regulators, has raised the concern that "the current application of regulations and controls may not always translate or address the unique public health risks posed by SaMD nor assure an appropriate balance between patient/consumer protection and promotion of public health by facilitating innovation."[4]

USP shares the aforementioned concerns regarding quality assessment of DTx. This paper therefore proposes a role for public standards in assuring product quality for DTx. The following concepts regarding how USP's quality framework for medicines may be applicable to these emerging therapies is intended to serve as an initial thought starter for further, open discussion. It is important to understand that any USP quality standards, documentary or physical, would need to proceed through USP's established public process for development and evaluation prior to official adoption.

Examples of Digital Therapeutics

There are several examples of Digital Therapeutic products on the market, including Pear Therapeutics' reSET, which was cleared in 2017 by the FDA as a treatment for substance abuse through the de novo premarket notification 510(k) pathway for medical devices. Recently Akili Interactive Labs Inc., received clearance for Endeavor™ (AKL-T01), for the treatment of children with attention-deficit/hyperactivity disorder (ADHD).

Defining Digital Therapeutics

To date, the term "Digital Therapeutics" can refer to several modalities within an overarching definition. The Digital Therapeutics Alliance defines DTx as "being able to deliver evidence-based therapeutic interventions that are driven by high-quality software programs to prevent, manage, or treat a medical disorder or disease. They are used independently or together with medications, devices, or other therapies to optimize patient care and health outcomes."[5] DTx can either be used in combination with traditional medication or can be the treatment itself. Some DTx developers utilize a more rigorous definition and as such, their products may incorporate randomized clinical trials, clinical evidence in support of filed claims, and safety and efficacy data to provide the evidence as required by the appropriate regulatory authorities. The concepts presented in this paper can apply to the broad category of DTx, and we will focus our discussion on the need and value of public standards for this ever-evolving field of DTx.

The Value of Public Standards

Public standards are developed through a transparent and collaborative process. They form the common foundation for assessing product quality across stakeholders, including manufacturers, patients, and healthcare providers.

Public standards are developed through collaboration with industry, regulatory bodies, and other relevant thought leaders. Public standards form a common foundation of quality that industry can build on to further innovate new products, while maintaining quality and public trust in marketed products. This is evidenced by the large number of standard setting organizations (e.g., Health Level Seven International, IEEE, International Organization for Standardization, National Institute of Standards and Technology, National Quality Forum, USP) that promote and define quality in their specific areas and applications.

Public standards have proven to be necessary, effective, and essential to support regulatory oversight of marketed products. In a recent literature review of the impact of USP standards on healthcare quality, Heyward showed that providing stakeholders with a common foundation of quality enables consistency across manufacturers and aids in the regulatory process by providing a common ground for assessment by the relevant agencies.[6] In addition, the use of USP standards enhances trust in products and their production, thereby ensuring quality of drugs in the U.S. and around the world. By providing this foundation of quality, the use of standards also has a positive impact on innovation and market competition by enabling organizations to differentiate themselves while maintaining quality. This has been especially vital in the medical field by helping to ensure the public's trust in recognized medical interventions.

Public standards are not stagnant. They reflect the best practices of the day and provide a process for capturing the new quality paradigms that emerge. As manufacturing technologies advance, so too do quality assessment techniques. For example, in reviewing the FDA Medical Device Recall Database from January 2002 to the first quarter of 2020, more than 500 recalls were linked to software and software-related failures, which could have benefited from public quality standards; of these recalls, more than 450 were designated as Class II devices. The reasons provided for recalls are wide ranging and include:

1. software security vulnerability
2. failure to alert patient for scheduled dosing
3. upgrades that reset patient parameters to default settings,
4. upgrade that included unapproved code changes
5. failure to correctly calculate the next required dose.

Public standards support good supply chain management and discourage illicit behavior. They promote the public good.

The FDA and other regulatory agencies use public standards, along with other appropriate guidelines, for conformance assessment of various quality attributes and function of the product under review. The availability and use of USP standards by the regulatory agencies provide for consistent review and assessment of quality across manufacturers. This provides for the assessment of equivalency between drug products as well as the ingredients they contain. Among the many benefits of using USP reference standards are the increased safeguards for the identification, determination of potential of contamination and demonstration of purity of the ingredients.

Having appropriate standards makes it possible to prevent, detect, and respond to product contamination, misbranding, and other forms of behavior that result in poor quality. For example, FDA mentions incidents with Heparin[7] and Melamine[8,9] as explicit examples of economic adulteration. In these examples, having the appropriate standard(s) and testing protocols allowed both the industry and regulators to better assess the quality of the product and to detect adulteration. This underscores the need for those standards to align with current technology and capabilities. In the digital age, there are additional quality concerns that industry and regulators must contend with including safeguarding privacy and confidentiality. These issues are especially relevant to DTx that access personal health information.

FDA's Center for Devices and Radiological Health (CDRH) recently provided its perspective on the value of public standards. In a presentation, a member of the CDRH

Standards and Conformity Assessment Program noted that public standards:[10]

- Promote international trade
- Are expeditious as they allow the reliance on consensus-driven standards rather than lengthy legal or rulemaking approaches
- Encourage innovation and competition among product developers
- Reduce burden on device companies by harmonizing expectations across international jurisdictions
- Speed the premarketing review process through:
  - Standardized conformance assessments and test reporting
  - Less time needed for "one-off" evaluations and requests for additional information
- Promote regulatory science at national and international levels
- Ensure that patients have access to innovative products that are safe and effective by optimizing "bench to bedside" time

Such standards provide value throughout the total product lifecycle including research and development, manufacturing, regulatory approval, quality control, assurance and testing, and post market surveillance. In its proposed regulatory framework, CDRH noted that standards are especially important with the evolution of digital medicine, stating: "The highly iterative, autonomous, and adaptive nature of these tools requires a new, total product lifecycle [TPLC] regulatory approach that facilitates a rapid cycle of product improvement and allows these devices to continually improve while providing effective safeguards."[10]

There is a lack of comparable and comprehensive public standards for DTx.

Public standards are important in the evaluation and approval of current therapies, as evidenced by the FD&C Act requirements on the use of USP standards. Furthermore, CDRH relies on USP and other standards-setting organizations' conformity assessments for medical devices. Currently, CDRH recognizes more than 80 software/informatics standards as included in CDRH's Recognized Consensus Standards Database: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. However, these standards are not specific to the unique requirements of the DTx community. This quality/conformity assessment gap is expected to widen as DTx applicability evolves and expands into new treatment areas, the number of products increases, and DTx use by clinicians and their patients becomes more widespread. As a result, it will be increasingly difficult to ensure quality and build the trust needed for medical providers and the general public to fully accept and properly utilize the wide range of DTx.

In this paper, USP outlines its current thinking on how its established public processes can be applied to developing DTx quality standards. USP seeks an open dialogue with industry, regulatory authorities, and other stakeholders on these critical issues. This paper initiates the dialogue with a brief review of the pharmacopeial approach for setting public standards that help ensure the quality of medicines.

The pharmacopeial approach

Public standards establish criteria for products and ingredients (each known as an "article") that ensure they are what they purport to be, in name, chemical nature, purity, and other critical quality attributes. In the U.S., the legal definition of a "drug" includes the active pharmaceutical ingredient (API) and excipients. APIs are the molecules providing the desired therapeutic effect (or active ingredients), and excipients—considered inactive ingredients—are the other substances intentionally included in the drug product and necessary for the active ingredients to have their intended therapeutic effect. Note that the term "finished product" contains both the API and excipients in specific amounts (dosage) and has undergone all stages of production, including packaging in its final container. The specifications for release of the finished product must comply with applicable FDA requirements.[11]

For example, any substance claiming to be "ibuprofen" must meet *USP–NF* ibuprofen quality standards and specifications, including relevant labeling requirements, or risk being deemed adulterated, misbranded, or both under U.S. law. Correspondingly, any substance meeting the ibuprofen quality standards must be named "ibuprofen," or risk being deemed misbranded. By establishing this relationship, public standards clarify language that might otherwise be ambiguous. Precisely defining the characteristics and specifications of the drug and its ingredients is crucial to establishing and verifying the quality of the article. For traditional therapeutics, the value of doing so has been well established over the 200-year history of USP.

For DTx, we are not aware of an analogous framework considering active ingredients and excipients. Similar to traditional medicines, we propose that DTx also have an "active" code, or a digital Active Pharmaceutical Ingredient (dAPI), and other code that supports the dAPI or digital excipients. Digital excipients would include code that tends to be shared between applications, such as communications stacks and graphics libraries.

A common practice by the software development industry is to obtain reusable or shared code (digital excipient code) from third parties, who are not always known or easily identifiable (e.g., due to the numerous individual contributors to open source projects). Given their potential to be used in multiple contexts, products, and combinations, and their frequent lack of known or controlled provenance, digital excipients and their use would benefit from quality standards. Ensuring the quality of ingredients is critical to any manufacturing chain, especially one resulting in the manufacture of therapeutics, whether traditional or digital. Ultimately, it is the DTx developer's responsibility—as it is with any credible, trustworthy manufacturer—to assure that any code (ingredient) in the final product, including digital excipients obtained from third parties, meets appropriate quality requirements before releasing it to patients. Identifying and establishing critical quality attributes of digital excipients will help DTx developers confirm their integrity as well as the absence of harmful codes to patients.

The concepts of dAPIs and digital excipients establish a foundation for the pharmacopeial approach to standards development. This approach includes the development of documentary standards and appropriate physical reference standards that provide the framework, guidelines, and best practices for testing the identified quality attributes of compendial articles.

USP documentary standards comprise general chapters and monographs. General Chapters range from guidance on specific laboratory methods and instruments to requirements for labeling and packaging. Monographs are specific to an API, excipient, or the final drug product itself, including multiple dosage forms of the drug product, such as tablets and gel caps. Physical reference standards are extensively characterized materials that are specific to the actual chemical or biological entities indicated in the appropriate documentary standards and required in order perform the laboratory tests cited in the monograph or general chapter.

General Chapters

General Chapters often serve as a repository for broader information and content, beyond individual product specifications. They can include methods applicable to multiple monographs, thus providing an efficient means of cross-referencing within the compendium. General chapters are numbered. Chapters numbered above 1000 are always informational in nature, and they provide information that can be representative of best practices and principles of practice for aspects of the industry at a point in time, e.g., definitions of key terms, guidelines on activities related to quality test procedures. General chapters with numbers below 1000 prescribe mandatory requirements where they are cross-referenced in the compendium. Specifically, a chapter numbered below 1000 may be made "applicable" (or required) if referenced in *General Notices*, a monograph, or another below-1000 general chapter that is applicable to the article. Below-1000 chapters describe requirements in topic areas such as product storage, dispensing and packaging, pharmaceutical compounding, and nomenclature. General Chapters provide a cross-cutting, broadly applicable foundation on which quality manufacturing can be assured. For example, they establish reference terms and procedures outlining key quality attributes for industry, so that manufacturers adhere to the same terms and procedures throughout the industry.

With the emergence of the DTx industry, there is an opportunity to define common terms and processes to help ensure product quality across many types of DTx. If general chapters are developed for DTx, USP envisions that they will help to reduce regulatory uncertainty, lower learning curves, speed innovation and development, enhance trust, and ensure product quality.

The following sections outline the potential areas of focus for general chapter development.

Potential for a General Chapter on Data Security and Privacy

A USP General Chapter on data security and privacy could outline the responsibilities of a DTx developer in assuring the trustworthiness of data management. These could include topics such as: software input and output; temporary, working data; and configuration data. These data can and should be kept free from integrity degradation through error prevention, detection and correction protections. Threats include, but are not limited to, keyboard loggers, screen capture and recording functions, microphone and camera access, and other on-device functions. The general chapter

could codify these threats, elaborate classes of privacy risks, and establish testing and mitigation procedures.

One of the current concerns in the DTx industry is its relationship and adherence to current Health Insurance Portability and Accountability Act (HIPAA) requirements, which aims to protect patient information and privacy.[12] DTx product manufacturers may be recognized as covered entities under HIPAA. This has not changed. What has changed is the evolution from paper-based communications to digital communications. This transition does, at times, make complying with HIPAA difficult under current regulations. While this paper is not intended to address this crucial aspect, it is important to point out that is the responsibility of the DTx developer/manufacturer to assure patient privacy and conformance to HIPAA requirements in the U.S., as well as other privacy regulations that may apply to DTx manufacturers, such as the General Data Protection Regulation (GDPR), or similar laws in other regions.

Building the foundation for data security and privacy, from USP's view, is a prime example of the broad-reaching utility and effectiveness of a general chapter. In open collaboration with appropriate industry and regulatory representation, the pharmacopeial approach would develop appropriate general chapter(s) that would clearly state the security requirements and responsibilities of the various parties developing DTx, with respect to patients and other relevant stakeholders.

Potential for General Chapter(s) on DTx Integration and Usability

A general chapter could focus on how the DTx and its components work together within the platform environment. Though standards do exist in related fields, such as electronic health records (e.g., from Digital Imaging and Communications in Medicine, HL7, Object Management Group's Domain Level Task Force), there are no standards for addressing the integration of components of a DTx. The capability to assess integration issues is important when the DTx functions across platforms such as iOS or Android on smart phones and tablets, especially as platforms and firmware are continually being updated. Developing such standards would assure that the DTx continues to function as expected and deliver the intended therapeutic effect, similar to a medicine that becomes bioavailable as expected.

An important aspect of a DTx product is its capability to deliver the intended therapeutic effect to the patient in a safe and effective manner. One important aspect of this requirement is to ensure the patient can use the DTx correctly. In 2016, FDA published its guidance for industry on "Applying Human Factors and Usability Engineering to Medical Devices," to minimize potential use errors (i.e., inability to use the product) that may result in harm to the patient. Monitoring the use of DTx products could help assess whether they are used as intended and promote further innovation in the next generation of DTx and delivery tools. The FDA outlines human factors considerations, including usability engineering, on its webpage.[13]

At their core, DTx are software systems. Quality and safety of software systems are well-developed management disciplines in healthcare and other industries (e.g., aviation and nuclear power) where the margin of safety is very narrow. These standards have documentary requirements for specifications, designs, tests, models, and developed components. The importance and acceptance of such standards is evidenced by the number and breadth of standards-setting organizations in the medical device space. The FDA's Digital Health Software Pre-Certification Program (https://www.fda.gov/medical-devices/digital-health/digital-health-software-precertification-pre-cert-program) may also highlight the need for additional standards that are currently unavailable

In summary, general chapters are documentary standards that serve a wide range of purposes (e.g., instrument operations, labeling, packaging). USP proposes that general chapters be considered as an appropriate mechanism to establish standards, furthering a common baseline for assessing quality, and enabling innovation in the DTx space.

Monographs

Monographs define critical quality attributes and specifications for a drug ingredient or a drug product in four key areas: identity, strength, purity, and performance.

The following are the traditional pharmacopeial definitions for each:

- Identity defines what the article is (e.g., molecular definition).
- Strength defines how much of the article there is.
- Purity defines what other substances may be present—and in what amount—before the article is considered not to be of quality.
- Performance defines how to assess whether the article has the physical characteristics needed for it to deliver the expected therapeutic effect. For example, for oral tablets, performance is most commonly assessed through a dissolution test. This test evaluates whether the tablet can be expected to dissolve in the right place in the gut to enable delivery of the API to the patient.

The discussion that follows will define each of these attributes with respect to traditional therapeutics and attempt to define the same for DTx.v

Identity as a critical quality attribute

1. Identity

A drug with a name recognized in *USP–NF* must comply with the identity/identification requirements of its monograph or be deemed adulterated, misbranded, or both.

https://www.usp.org/about/legal-recognition/standard-categories

In a chemical medicine, identity is defined both in name (nomenclature) and physical characteristics. The product must have an official name that is unique to its physical nature (i.e., its chemical structure or other defining characteristics). For example, "ibuprofen" is defined by the chemical characteristics of the compound named ibuprofen. Any drug named "ibuprofen" must have that chemical structure or risk being deemed misbranded in accordance with the FD&C Act. To verify that an article named "ibuprofen" has the approved structure, the manufacturer must perform tests as outlined in the appropriate monograph and along with the correct physical reference standard. These tests confirm that the chemical does have the physical characteristics and conforms to the acceptance criteria of the Ibuprofen monograph.

Identity is not always straightforward for some molecules or combinations of molecules. For example, some growth factors are more easily and directly identified by their ability to affect specific cells in culture. Therefore, a means of addressing identity in some instances may be through a functional assay and potentially by other characteristics. For DTx, this concept of function also applies because it is inherent in the nature of the product. This is because it is the code's mode of action that is unique to the DTx product, not necessarily the code itself. Changing the code through revisions and/or improvements may not signal a need to be considered as a new DTx as the functional/mode of action is the same. Therefore, it is the function or output of the code that is in fact, its identity.

Given that simple code comparison is insufficient as the identity test for DTx, we propose functional testing as an alternative approach. Specifically, identity could be tested against a set of expected behaviors, inputs, and outputs for a DTx, its dAPI, and/or its digital excipients.

In addition to functional tests, identity may require examination of other characteristics of the code. For example, software is composed of input data streams such as arithmetic and other logical expressions, internal information and data models, control structures (e.g., if/then, subroutines), and internal structures (e.g., recurrent neural networks and associated learning algorithms). Following the mode of action of these inputs, a uniquely defined set of data outputs are generated. The specific combinations of some or all of these may create what is essentially a fingerprint of the DTx product. Would such a fingerprint and functional test(s) be sufficient to uniquely identify a DTx or its components while still allowing for minor changes in code? What other approaches could be explored to assess the compendial identity of a piece of software that was potentially developed by an unknown, or poorly identified, third party?

Strength as a critical quality attribute

2. Strength

The strength of a drug product is expressed on the container label [for chemicals] in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph.

Source: General Chapter <7> *Labeling* Currently Official.

Strength, in chemical medicines, is typically described as the concentration of the API (or drug ingredient) in a finished product or preparation. Strength tests are known as quantitative tests and are designed to determine how much of an API is in the drug product.14 This is important when comparing products purporting to be of different strengths (i.e., 200 mg ibuprofen compared to 600 mg ibuprofen). This concept of strength may be important for DTx in which there are multiple DTx available to the patient and medical provider. Is there a difference in the strengths such that one is more suitable for one patient population or another? If so, how can that strength be assessed for proper dosing? In order to address this question, it is first necessary to provide a working definition of "strength." For DTx products, strength can be envisioned in two key ways: 1) how much of the product is available to the patient and 2) how often does the

patient get exposed to the DTx product. These two points are not exclusive of each other.

In the first case, the question of "how much strength" does a DTx have, may seem nonsensical on the surface; however, software can be adapted to several uses through differential configurations of parameters. In this context, the notion of strength in a DTx refers to the specific configuration parameters applied that result in a specific behavior of the DTx. As an example, the speed with which one proceeds through the levels of an interactive experience is dictated by a ramp-up function in a core algorithm of the DTx, which could be configured differently based on the medical condition or the need of the individual patient being addressed. In the second case, the amount of time the patient interacts with or is exposed to the DTx may be the appropriate way to define strength of the DTx.

Additionally, these two concepts of strength can be intertwined through a multilevel DTx product. For example, how long it takes to move from one level to the next may be linked to the speed of code for that level. Also, the transition to the new level may be dependent on how often the patient interacts with the DTx to achieve/demonstrate the required behavior to move forward. This raises the question: if one level equals one "dose", and the levels increase in intensity along with the required time of exposure and required behavior, then is the "strength" and the "dose" also increasing?

Thus, the need to carefully define what is meant by strength. Returning to ibuprofen, a 200 milligram tablet is a 200-milligram tablet. Only by adding more of the API per final product increases the strength of that product, on an equal unit scale (per tablet). Increasing the patient's exposure (taking more tablets) does not increase the strength of each tablet but does increase the total amount of ibuprofen the patient is receiving.

If strength can be both a physical component (ramp time) and a patient interactive component (time of exposure) how can strength be quantified and compared across DTx products? Can the configuration parameters, such as ramp-up speed, be measured across DTx? Are there industry accepted evaluation methods for such assessments? Can these be comparable across different DTx or the same DTx with differing "strengths"? In addition, as revisions and updates occur throughout the lifecycle of the DTx, it is important to ensure that the strength is maintained and that the patient is receiving the intended dose. Are these measured in a predetermined time span to assess the physical component of strength? How does one measure the interactive component of strength?

Purity as a critical quality attribute

3. Purity

"...the purity of the material [is used] to confirm its homogeneity, to determine its suitability for use in the official applications."

Source: 2005-11-30 Todd L Cecil, USP - Senate testimony (page 47), delivered 2005-04-19 HELP committee, 109th congress, 20-814, Chairman ENZI.pdf.

For medicines, purity assesses whether there are any unexpected substances in a sample of an ingredient or product and, if so, whether the amounts are permissible and meet specifications. Most of the compendial standards discuss the tests for impurities and quantification and provide an acceptance range. The ability to assess purity and identify the presence of an impurity is critical to establishing the quality of a medicine. Purity as a critical attribute recognizes that substances other than the intended active ingredient and excipients may be present.15

Impurities can be generally defined as contaminants or adulterants. Contaminants are typically those entities that are inadvertently present in the article (e.g., due to an insufficient purification step). Examples of contaminants include organic and inorganic impurities as well as residual solvents.16

Adulteration often has an economic incentive. Adulterants are typically added to articles by disreputable actors aiming to deceive regulators, resellers, healthcare providers, and patients. Typically, these purposefully added materials attempt to either provide a false identity of the drug product in question or to make the drug product seem stronger than it is.

Purity of DTx could be compromised by 1) the presence of errors (bugs) that may degrade performance and 2) undesirable behavior, malicious or innocent, akin to adulterants and contaminants. Examples include leaking of (meta)data to unexpected parties, computer viruses or malware impacting the DTx directly, and undesirable code (such as resource starvation by another program running on the operating or networking system) destabilizing, degrading, or otherwise negatively impacting a DTx.

USP proposes assessing the purity of a DTx and/or its components by ensuring a lack of unwanted software code or "effects" in the article. Purity assessment could build on the extensive experience of the antivirus/antimalware industry. USP proposes that there is no acceptable level of "malicious" impurities.

Performance as a critical quality attribute

4. Performance

"Drug product performance, in vivo, may be defined as the release of the drug substance from the drug product leading to bioavailability of the drug substance."

Source: Applied Biopharmaceutics & Pharmacokinetics, Sixth Edition 2012 (Leon Shargel, Susanna Wu-Pong and Andrew Yu) Chapter 15: Drug Product Performance, In Vivo: Bioavailability and Bioequivalence.

In the pharmacopeial approach, performance can be defined as whether the article (marketed drug product) has the physical characteristics needed to deliver the expected therapeutic effect at its target site. This definition is not intended to infer any measure of clinical outcome, such as safety or efficacy.

As we have noted above, performance in chemical medicines is most closely associated with dissolution.

How, then, can the performance of a DTx product or its components be defined and measured? Are there equivalent or nearly equivalent concepts in the DTx world? Could compendial performance be assessed, for example, as measures of the reaction time of an algorithm or refresh rate of a graphics library? Are there testing methods or assessment methodologies that provide evidence that when used properly the unique algorithm(s) of the active code become available to the patient? Notably, in addition to simply being able to measure these key attributes, it is important to demonstrate the consistency of the DTx product performance throughout its lifecycle.

In summary, monographs are documentary standards that explicitly define and specify critical quality attributes for the drug product and its API and excipients components. In addition, the monograph provides testing procedures and specifications that must be met in order for a drug to be legally marketed in the U.S.

Potential Monographs for DTx

Value of Ingredient Monographs for DTx

As previously described, a DTx product consists of both dAPI and digital excipients, each of which can be the subject of a monograph. Given that there are not, as far as USP knows, multiple manufacturers for the same or equivalent dAPI, USP proposes that establishing dAPI standards may not be appropriate at this time. Instead, digital excipients would be the initial focus of ingredient monographs. This will help establish a quality foundation for DTx and help address issues industry faces around software of unknown provenance (SOUP).

Digital excipients are essential, but they do not typically provide a distinct and competitive advantage. Standardizing them in monographs may reduce the cost, complexity, and other risks of including SOUP or other reusable components in DTx, especially when seemingly equivalent digital excipients are made available by different developers. Digital excipient monographs could provide common standards to ensure that code functions as it is supposed to, even when it is not produced by the DTx developer. Furthermore, they could help ensure that the code does not interfere with the dAPI or introduce digital impurities.

Example of a potential General Chapter and ingredient Monograph

Imagine a scenario in which several software developers create similar but different data access code libraries for DTx developers to choose from. For example, an internet search of "C SQL library" produced a plethora of distinct Structured Query Language (SQL) libraries, each of which could be a digital excipient with slightly different behaviors. In this example, a general chapter could be developed for the DTx industry that defines the overarching characteristics of data access or specific SQL libraries. This documentary standard would define and describe the attributes of generic data access libraries and their critical quality attributes. An excipient monograph would define and describe the quality parameters of a single data access excipient code with mandatory testing requirements. The value would be in helping the DTx developer ensure the identity and performance of the excipient code used in its DTx.

Conclusion

The framework described in this paper has been developed by USP over 200 years and has proven effective and flexible enough to accommodate more than 4,000 public standards across multiple therapeutic types. This framework has established an objective, third-party source of explicit pharmacopeial requirements to help determine and assess quality of ingredients and products. USP public standards establish trust and assure quality, especially in marketplaces with multiple manufacturers producing articles having identical critical quality attributes. In so doing, they reduce regulatory uncertainty and improve credibility of an industry. With some modifications and adaptations for DTx, this framework has the potential to enhance the quality, growth, and speed of adoption of the DTx industry.

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Acknowledgements

Megan Coder, Executive Director, Digital Therapeutic Alliance.

Yuri Maricich, Chief Medical Officer, Pear Therapeutics.

Jeff Abraham, Vice President, Head of Commercial Market Access and Trade, Akili Interactive.

Joseph Bormel, MD, MPH