IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

1500 K Street NW • Washington DC • 20005
Telephone +1 202 230 5607 • Fax +1 202 842 8465
Email info@ipacrs.org • Web www.ipacrs.org

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IPAC-RS COMMENTS ON THE USP WHITEPAPER
"THE ROLE OF PUBLIC STANDARDS IN ASSURING QUALITY OF DIGITAL THERAPEUTICS"[1, 2]

For submission by email to: DTxWhitePaper@usp.org

The International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) commends USP and the Digital Therapeutics Alliance (DTA) for preparing and issuing for public consultation the paper entitled "THE ROLE OF PUBLIC STANDARDS IN ASSURING QUALITY OF DIGITAL THERAPEUTICS".

IPAC-RS is a non-profit association of companies that develop, manufacture or market pharmaceutical products for delivery via respiratory tract - such as metered dose inhalers (MDIs), dry powder inhalers (DPIs), nasal sprays, and other product types - with the goal of advancing science-based and data-based regulations, standards, and practices for these products. A list of current members, and further information are available at http://ipacrs.org.

A thoughtful approach to digital therapeutics and to quality standards is now more important than ever. IPAC-RS appreciates, therefore, the opportunity to provide the general and page-by-page comments that follow. Furthermore, IPAC-RS would be willing to engage in more interactive collaborative discussions with USP and DTA, as appropriate. IPAC-RS members also look forward to the public workshop in the Fall of 2020, as announced by USP[2].

[1] Michael Ambrose, Danielle Seiler, Brandon Barrett, Christine Yu, Doug Podolsky, Michael Levy. The role of public standards in assuring quality of digital therapeutics. https://qualitymatters.usp.org/sites/default/files/user-uploaded-files/USP_Digital_Therapeutics_Paper_2020-06-11.pdf (June 2020)

[2] USP announcement of the USP/DTA whitepaper. Quality Concerns and Future Steps into the Era of "Digital Medicines" https://qualitymatters.usp.org/quality-concerns-and-future-steps-era-digital-medicines (June 16, 2020)

GENERAL COMMENTS

USP is to be applauded for forging the path towards the development of standards for "Digital Therapeutics" (DTx). At the same time, it is debatable whether placing DTx into a USP model is a logical fit. Some challenges, as well as positive aspects of this approach, are discussed below.

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."

Role of Standards

It is good to have standards to follow, however there is concern that creation of new standards may restrict ability to utilize creative and novel, yet compliant, approaches to ensuring performance. Since the standards might unintentionally restrict creativity or novel approaches, would it be better to consider that sponsors of medical products instead follow an appropriate quality system for design, development and manufacturing? Furthermore, product sponsors should uphold the quality system requirements with their vendors that generate any software code used in the product. An example may be requiring the utilization of design controls via ISO 13485. Three of the five examples offered in the USP/DTA paper of the 450 recalls from the review of the US Food and Drug Administration (FDA) Medical Device Recall Database from January 2002 through first quarter of 2020 appeared to be possibly linked to upgrades which could also be considered design changes. Perhaps a design change review for the upgrades in items 1, 3, 4 would address the recalls related to the listed items.

Standards should be aligned to the software field. Utilizing USP's mission for development of standards that ensure quality, safety, and benefit of medicines and foods may result in alternate directions or even misalignment to existing software standards. For example, one software standard, IEC 62304, is a recognized consensus standard for software life cycle processes in medical devices. Other FDA guidances (see the text box below) exist to describe the requirements for software use in medical devices. The whitepaper mentions more than 80 software/informatics standards included in FDA CDRH's Recognized Consensus Standards Database but concern is raised within the whitepaper that these standards do not meet the requirements of the DTx community. Also mentioned in the whitepaper is that this quality/conformity assessment gap is expected to widen as DTx applicability evolves and expands into new treatment areas with the number of products increasing and use by clinicians and patients becoming more widespread.

Avoid Duplication

All drug-device combination products are regulated by an appropriate agency (such as the Food and Drug Administration in the U.S.), are required to go through a rigorous development, review and approval process before they ever reach the market. In light of the already-existing regulatory framework, an additional set of information in the USP has a high chance of being redundant and duplicative, at best, or divergent and contradictory to FDA's positions, at worst. For example, the USP/DTA whitepaper focuses on 'generic' repeatability of coding. However, the FDA's 510(k) established approval pathway already provides substantial equivalence criteria but retains the ability to tailor the software without compromising patient safety. These overlaps and misalignments may further accumulate over time as each organization (FDA vs USP) continues to issue new and revised guidelines independently of the other.

Pros and Cons of Applying CQA Concepts to DTx

The application of a Critical Quality Attribute (CQA) approach mentioned in the whitepaper itemizes quality attributes of digital therapeutics systems to be synonymous with Identity, Strength, Purity, and Performance. The fit of traditional medicines CQA framework to digital therapeutics complicates the terminology and does not match well, requiring translation in order to be interpreted. The one concept in this framework that deems consideration is 'digital excipients' insofar as it would apply to Custom off-the-shelf (COTS) and Software of unknown pedigree (SOUP) which are accepted concepts in the culture of programmers but not really aligned to the philosophy of the pharma or medical device industries. While the term 'digital excipients' may not be the best term, the concept of utilization of common code to be used in multiple applications and the need for a repository or 'library' of authorized codes has some merit. The challenges with this concept will be how to remain relevant and updating of applicable standards in the quickly changing world of software. In addition, the speed of change and development in digital would mean that any additional guidance applied in USP may quickly become outdated and the main focus should therefore be on the end combination product/device, and cross-referencing the existing guidance and standards (many of which are referenced in this document).

EXAMPLES OF US FDA GUIDANCES DESCRIBING REQUIREMENTS FOR REGULATED SOFTWARE USED IN MEDICAL DEVICES

Title	Issued	Link
FDA. Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submission for Software Contained in Medical Devices.	May 2005	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-content-premarket-submissions-software-contained-medical-devices
FDA. Guidance for Industry, FDA Reviewers and Compliance on Off-the-shelf Software use in Medical Devices.	September 2019	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/shelf-software-use-medical-devices
FDA. General Principles of Software Validation; Final guidance for Industry and FDA Staff.	January 2002	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-principles-software-validation
FDA. Guidance for Industry: Cybersecurity for Networked Medical Devices containing Off-the-Shelf (OTS) Software.	January 2005	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cybersecurity-networked-medical-devices-containing-shelf-ots-software
FDA. Content of Premarket Submissions for Management of Cybersecurity in Medical Devices: guidance for Industry and Food and Drug Administration Staff.	Final October 2014 New draft October 2018	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices-0 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-premarket-submissions-management-cybersecurity-medical-devices

A Harmonized Approach Is Needed

An additional consideration in the creation of a USP content related to digital medicines is a potential lack of harmonization. The pharmaceutical and medical device industry, in particular the developers and manufacturers of drug-device combination products, are already struggling to understand and implement the divergent global requirements across the regulatory and standards landscape. At this time, the industry is in significant need of global harmonization in the digital space, and, therefore, development of USP requirements in isolation from other standard-setting agencies is unlikely to improve the regulatory and standards landscape. Further, some areas covered by the USP proposal (e.g. off-the-shelf software, cybersecurity, usability) include elements that initially seem divergent to guidances, frameworks, and consensus standards that already exist which might create additional complexities for industry and regulators.

Overall, therefore, while IPAC-RS acknowledges USP's interest in digital therapeutics and applauds the USP/DTA initiative in this space, the timing of this effort needs to be synchronized with broader developments. In particular, given the relatively immature state of the digital therapeutics field, the emerging nature of regulations from FDA and other health authorities, as well as the numerous available and in-progress consensus standards in the area of medical device software development and clinical evaluation, IPAC-RS respectfully suggests that development of pharmacopoeial standards in the area of digital medicines may be premature.

Some Areas Could Be Addressed Even Now

Although IPAC-RS questions the benefit of USP-specific standards on digital medicines at this time, there is a real and current need for clarification on the non-proprietary naming conventions for digital therapeutics when they include a medicine. Under USP's role in pharmaceutical naming it would be of great benefit to work collaboratively with industry and regulators on the development of non-proprietary names for digital components. For example, specifying the language a pharmaceutical or drug-led combination product may use when naming an inhaler with a digital component might include "with sensor" or placing an "e-" prefix to indicate electronic capabilities.

PAGE-BY-PAGE COMMENTS:

Page 4. The recall database goes from 2002 to 1Q20, which seems a very wide timespan for software, with less relevance in the earlier part of that period. Suggest narrowing the window to 2010-1Q20 or even 2014-1Q20 to reflect more of the current state.

Page 5: The reference to "Total Product Lifecycle" does not include product decommissioning, which for DTx software is a critical phase of the lifecycle and can have significant impact on healthcare providers and patients.

Page 6: The pharmacopoeial approach for drugs does not directly translate to DTx, in part because the "dAPI" for DTx can be a combination of functionalities, some regulated and some not. Each related DTxx product may have a different combination of these functionalities.

Page 7: Proposed General Chapter on Data Security and privacy seems to overlap with the proposed Chapter 3 about "Purity," and vice versa.

Page 7: The "Potential for General Chapters..." section refers to "platforms such as iOS or Android on smartphones or tablets" but mentions neither websites with DTx functionality nor software in the cloud.

Page 8: Same comment as for Page 6 above.

Page 9: Application of the term strength to DTx does not flow as it is in the paper, when the strength of the DTx really corresponds to the supportive clinical evidence for the software.

Page 9: Purity used in this way does not appear to account for rapid software updates as part of change management; and neither does it account for the variety of device types and their ages where software will be running.

Page 10: Performance in this section does not refer to DTx safety or efficacy, but to technical aspects of software performance. These technical aspects are less relevant if the software does not meet its expected safety and efficacy goals. For example, if the software algorithms run quickly, and the graphics refresh rapidly, but the resulting clinical impact on the patient is not as expected, then how can the USP "standard" say that the software is performing well?

CONCLUDING RECOMMENDATIONS

A more comprehensive whitepaper on the existing software standards and guidances intended for consideration when developing a digital therapeutics device would be a good first step in developing the holistic approach that USP is proposing. This would utilize the expertise from software standards committees to drive what gaps, if any, exist in the development of combination products that use digital therapeutics applications. It is recommended to begin this summary prior to enacting a new framework to fit new standards as the existing standards may provide the needed terminology, framework and requirements.

IPAC-RS remains highly interested in this topic and would welcome an opportunity to discuss these comments and related issues with USP and DTA further, e.g., through workshop(s) and/or interactive webinars. IPAC-RS looks forward to the revised draft and the forthcoming workshop.

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