Regulatory challenges to the advancement of AI-enabled personalized chronotherapy in precision oncology

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BACKGROUND

Personalized chronotherapy (PCT) aims to synchronize drug administration with the body's natural 24-hour circadian cycle, aligning target receptor/gene expression. This approach seeks to enhance treatment effectiveness through an optimized timing of dose administration - minimizing toxicity and leveraging circadian influences on drug metabolism, cell cycle regulation, and DNA repair [1]. Indeed, several randomized control trials for breast, colorectal, and endometrial cancer evaluating the timing of treatment showed reduced side effects including mucositis, stomatitis, and leukopenia [2]. Moreover, recent studies indicate that chronotherapy not only improves tolerance during chemotherapy but also, in some cases, enhances survival with both chemotherapy and immunotherapy [3][4][5]. These findings are currently used to personalize treatments based on gender and circadian clock markers [1].

Despite potential benefits of PCT, its development has faced challenges due to the variability in individual circadian rhythms and the need for reliable and targeted drug delivery systems. But in today's digital age, the integration of non-invasive sensors, wearables, internet of things and artificial intelligence (AI)-driven algorithms presents a significant advancement to enable chronotherapy. This shift is illustrated in the French MultiDom clinical study [6], where pancreatic cancer patients undergo continuous telemonitoring of circadian rhythms through connected non-invasive devices and electronic patient-reported outcomes questionnaires. All data are tele-transmitted and automatically analyzed every day, with the goal of reducing toxicity-related emergency hospitalizations to less than 10%.

As the correct dose and schedule are the foundation of drug development, the Oncology Center of Excellence (OCE) in FDA has started "Project Optimus" initiative in the aim to reform the dose optimization and dose selection paradigm in oncology. However, integrating precise, personalized, and automated technologies to advance PCT still presents several challenges, from the development of standardized and integrated technical solutions to the medico-economic and organizational aspects of PCT integration into healthcare systems.

OBJECTIVES

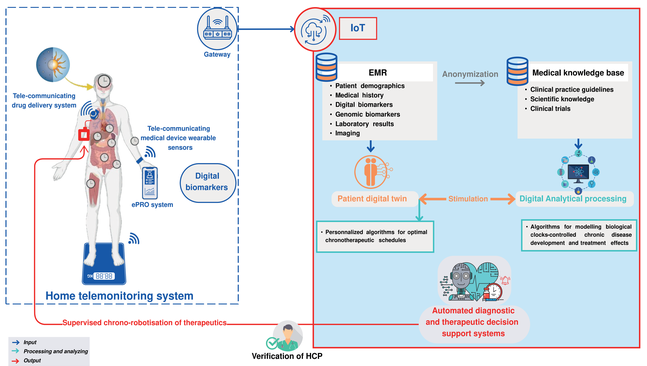
1. Investigate the development of Personalized Chronotherapy (PCT) in precision oncology, identifying the different components – current and foreseen (technological advancements)
2. Decompose and analyze regulatory challenges related to such single/integrated AI-enabled multi-component PCT systems.
3. Provide preliminary insights based on the analysis of existing AI-based devices in other applications to tackle the identified regulatory barriers.

METHODOLOGY

1. Identify and categorize various components crucial to the PCT system in oncology.
2. Conduct a comparative analysis of EU and FDA regulatory frameworks related to PCT components, specifying challenges of each component.
3. Highlight specific challenges related to AI-enabled multi-component systems.
4. Extract insights from market-available devices, particularly in diabetes.

RESULTS

Figure 1: *An integrated vision for AI-enabled Personalized Chronotherapy System*



Remark: Diabetes devices are combined drug-device products, while in oncology, such combinations do not currently exist due to the significant variability in treatments

Figure 2: *MultiDom study using a circadian telemonitoring-telecare platform in patients at home [6]*

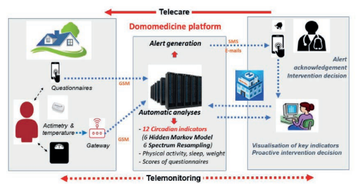


Diagram showing the connectivity between the thoracic sensor, the scale, the home-based data collection device, the electronic tablet in the patient's environment (left panel), the central data hub, with its resident automatic programs (middle panel), and the oncology team (right panel). GSM, Global System for Mobile communications; SMS, Short Message Service.

Figure 3: *Examples of market-available devices for precision medicine in diabetes and oncology*

Automatic Insulin Delivery - iLet Bionic Pancreas

It is an FDA-approved system which combines the iLet ACE Pump and iLet Dosing Decision Software, both regulated by the **510(K) premarket clearance pathway.** Using an algorithm, it optimizes insulin delivery.

Automatic Insulin Delivery - t:Slim X2 pump

It is an FDA-approved system granted under the FDA's **de novo pathway,** which is used for innovative medical devices that do not have a legally marked predicate device. It's the first insulin pump to be approved for use with Control-IQ technology, which is an algorithm that automatically adjusts insulin delivery based on glucose readings from a continuous glucose monitor (CGM).

Remote care management – Current Health

This platform unifies **CE marked class IIa remote patient monitoring devices and telehealth.** It uses machine learning algorithms to analyse patient data and identify potential health concerns. It is also Cyber Essentials, Cyber Essentials Plus, ISO 27001, ISO 13485, DTAC and DSPT certified.

AI breast cancer diagnostic - RlapsRisk BC

It is an **AI prognostic CE-IVD** solution that predicts whether a breast cancer patient (ER+/HER2-) will go on to relapse after treatment, informing oncologists which high-risk patients may benefit from targeted therapies and which low-risk patients could potentially avoid chemotherapy.

Table 1: *Comparative analysis of EU and FDA regulatory frameworks related to PCT components and regulatory challenges of each*

(*Current regulatory classification)

Component *	Description / Role	FDA regulation	EU regulation	Regulatory challenges	Development status: examples and references
Tele-communicating intelligent drug delivery system (Combination product)	A drug delivery pump or system, composed of the administration device and the drug itself, to administer cancer treatment under a personalized chrono-modulated schedule. It should be able to share in real time the delivery data and to adapt or stop administration in case of specific patient or environment contexts.	It involves determining the primary mode of action (PMOA) for combination products, with sponsors having the option to seek formal assignment through the Request for Designation (RFG) process or obtain informal feedback via the Pre-RFD submission. There is a lack of explicit guidance.	These systems fall into a borderline classification, introducing uncertainty in the regulatory framework. National authorities categorize them as medicines or medical devices based on their primary mode of action on a case-by-case basis, leading to an overall environment of regulatory ambiguity.	Complex stimulus-sensitive nano-drug delivery systems face difficulties in obtaining approval for clinical use. The regulatory landscape lacks an integrated approach to oversee all components of the system.	*There is no such market-available system in PCT oncology today.* ***In diabetes:*** **Automated insulin pump system using advanced hybrid closed-loop algorithm (FDA approved and CE marked): MiniMed™ 780G system** **Zhang, J., Xu, J., Lim, J., Nolan, J. K., Lee, H., & Lee, C. H. (2021). Wearable glucose monitoring and implantable drug delivery systems for diabetes management. Advanced Healthcare Materials, 10(17), 2100194.**
Tele-communicating wearable sensors (Medical device)	Wearable (and preferably non-invasive) sensors that continuously monitor and transmit patient's health data such as actimetry, weight and temperature. Some of these data – such as actimetry and body temperature – allow to monitor the individual patient's circadian rhythms.	The FDA released guidance focused on non-invasive remote monitoring devices for patient care, clarifying enforcement policies and premarket expectations post-COVID-19. Class I and II devices often follow the 510(k) process, demonstrating equivalence to marketed devices. Class III devices, posing higher risks, undergo a rigorous premarket approval (PMA) process.	A pivotal study is mandated when literature evidence falls short for CE certification. Adherence to medical device regulation (MDR) and General Data Protection Regulation (GDPR) are key elements in ensuring regulatory compliance and patient safety.	The lack of clear guidelines and standards for wearable sensor technology, illustrated by the following questions: • For a number of devices, there is often a close continuity between selfcare, research and medical purpose, which need to be addressed by the manufacturer in its intended use; • For a number of data obtained from non-invasive sensors, there is a need to demonstrate the correlation with physiological validated biomarkers (see the Digital Biomarkers component); • The richness of data from remote monitoring devices requires the development of novel statistical methodologies.	**A wearable breast health monitoring device, using Machine learning and data mining (under clinical trials): Cyrcadia Breast Monitor** ***Royea, R., Buckman, K. J., Benardis, M., Holmes, J., Fletcher, R. L., Ng, E. Y. K., ... & Ellenhorn, J. D. (2020). An introduction to the Cyrcadia Breast Monitor: A wearable breast health monitoring device. Computer methods and programs in biomedicine, 197, 105758.***
Digital biomarkers (No clear classification)	Digital biomarkers encompass quantifiable indicators sourced from technologies like real-time monitoring devices and genomic sequencing.	The FDA's BEST Group provides a formal definition for digital biomarkers, emphasizing their validation in relevant contexts of use. The regulation underscores the importance of patient-generated health data (PGHD) in near-term research areas, as outlined in the FDA DHCoE RS Spotlight from October 2022.	EMA has defined digital biomarkers in its 2020 draft guidance "Questions and answers: Qualification of digital technology-based methodologies to support approval of medicinal products". It distinguishes them from electronic clinical outcome assessments (eCOA). It also recommends two key qualification documents: Qualification Advice for early stages, with an optional letter of support for promising but not fully qualified methodologies, and Qualification Opinion for Public Consultation, involving a broad consultation process and occasional workshops for stakeholder input.	The lack of clear definitions for biomarkers, particularly in delineating the specific applications of the term "digital biomarker". The lack of clear classification criteria introduces ambiguity in regulatory frameworks, impacting the development and approval of digital biomarkers. The lack of clarity in distinguishing measurement methods, encompassing wearables for biological biomarkers and behavioral data recording, impedes regulatory understanding of digital biomarkers' reliability and distinct characteristics.	**AI-supported digital biomarkers solutions and mathematical tools for clinical selection of effective immune therapeutics** ***Huss, R., Raffler, J., & Märkl, B. (2023). Artificial intelligence and digital biomarker in precision pathology guiding immune therapy selection and precision oncology. Cancer Reports, e1796.*** **Circadian biomarkers collected from a wearable device** ***Zhang, Y., Cordina-Duverger, E., Komarzynski, S., Attari, A. M., Huang, Q., Aristizabal, G., ... & Levi, F. (2022). Digital circadian and sleep health in individual hospital shift workers: a cross sectional telemonitoring study. EBioMedicine, 81.***
Patient digital twin (DT) (Software as medical device (SaMD))	Patient digital twin uses computational models to replicate individuals, integrating genetics and lifestyle data to optimize the timing of medical interventions.	Broad concept flexible DTs have not been implemented in practice and comprehensive realization of the DT concept is precluded under current regulatory frameworks, as these require the pre-specification of device intended purpose.			**Mathematical model of the circadian clock and drug pharmacology** ***Hesse, J., Martinelli, J., Aboumanify, O., Ballesta, A., & Relógio, A. (2021). A mathematical model of the circadian clock and drug pharmacology to optimize irinotecan administration timing in colorectal cancer. Computational and Structural Biotechnology Journal, 19, 5170-5183..***
Clinical decision support systems (CDSS) to propose automated support for diagnostic and therapeutic decisions (Software as medical device (SaMD))	CDSS provide diagnosis and/or personalised treatment suggestions, informing or driving treatment, based on individual patient physiological and clinical data	The FDA has issued guidance on predetermined change control plans (PCCPS) for managing and controlling changes to AI–powered CDSS through their lifecycle. It has also defined "Clinical Decision Support Software" guidance which provides examples of how FDA applies the Non-Device CDS criteria.	According to the MDR, if a CDSS is used to guide the treatment of the patient, it will either belong to class IIa, IIb or III depending on how developers describe and notified bodies evaluate the intended use. Aligned with EU goals, MHRA's AIaMD program aims to proactively aids companies in efficiently launching safe, effective AI-enabled medical devices.	The assessment of classification is objective, given the absence of a clear delineation in the classification of CDSS. Lack of transparency and interoperability in most of AI-based CDSS, limiting the adoption, trust, and practical usability of these systems.	**A complete mathematical framework to optimize drug infusion pumps and inform on inter-patient pharmacokinetics variability** ***Hill, R. J., Innominato, P. F., Lévi, F., & Ballesta, A. (2020). Optimizing circadian drug infusion schedules towards personalized cancer chronotherapy. PLoS Computational Biology, 16(1), e1007218.***

CONCLUSIONS

1. Today, the only «smart and integrated» drug-device for personalized autonomous treatment administration can be found in diabetes, as there is only one common drug; whereas in oncology PCT, drugs may include a range of different types of medications, such as chemotherapy, agent, targeted therapies, immunotherapies, and hormone therapies.
2. None of market-available automated insulin pumps or what is also called artificial pancreatic use AI.
3. The first systems on the market for oncology PCT would be telemonitoring systems composed of sensors and software (medical devices, potentially AI-enabled).
4. Current regulatory frameworks orient toward the development of specific systems for particular cancer types (as they rely on specific intended use and PMOA).
5. Regulatory fragmentation occurs due to the separate regulatory treatment of medicines and devices, despite their integrated use in practice.
6. Regulatory frameworks might not be updated to reflect the state of art in technology or practice. Therefore, there is a need for fast-track programs.
7. There are still scientific, technological, and regulatory inter-related questions to be addressed for an integrated vision of PCT, such as the development of drug-delivery innovative systems for new oncology therapies, the validation and use of digital biomarkers - not only for drug development, but also for treatment monitoring in clinical practice, and the development and validation of a personalized patient circadian digital twin.

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