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PharmaLedger a Blockchain-enabled Healthcare Platform

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***Abstract*—This article presents human-centric healthcare solutions that could revolutionize the medical sector by creating trust with the help of blockchain technologies. This article summarizes the experience of creating a blockchain platform and a Digital Trust Ecosystem in a private-public partnership between research entities and ten big pharma companies. This partnership builds on a previous research project that pioneered the OpenDSU blockchain technology. This article summarizes the research results obtained in blockchain technologies under the influence of the pharma industry culture and regulations.**

Keywords—blockchain; human-centric; healthcare; pharma; eLeaflet; supply chain; anti-counterfeiting; personalized medicine

I. INTRODUCTION

The transition from the analog world to the digital world represents one of the greatest advances in technology. The evolution of mankind is increasingly accelerated, the quality of life is constantly increasing, and the demands and needs of people are ever greater. Every aspect of life tends to be revolutionized and integrated with the help of digital technologies. In this sense, one of the recent digital revolutions is represented by Blockchain technology.

Blockchain technology was introduced in 2008 [1] as a technology that, without a trusted intermediary, should be tamper-proof and publicly or privately available. The data that is written to a blockchain ledger may vary depending on the system and/or solution implemented. The type of data written to a blockchain ledger can be: cryptographically signed event data, cryptographic hashes of data with minimal relevance, cryptographic hashes of data and a pointer to off-chain data, combinations thereof, or many such methods.

Blockchain as middleware, due to its properties of non-repudiation, immutability, and traceability, can be a cornerstone in the development of future applications. With the help of the integration of this technology, middlemen can be eliminated and authenticity, integrity, privacy, and decentralization of data could coexist. In this regard, a recent survey found that half of Americans have decided not to use a product or service because of privacy concerns [2].

The role of this technology is to increase the trust of all participants, whether we are talking about companies or consumers. The basic, fundamental objective is to increase the safety and quality of life of end consumers by offering products or services that meet current concerns and needs.

After briefly pointing out the aspects related to blockchain technology, respectively, examples of how it serves as "middleware" for trust, this paper highlights the blockchain in the pharmaceutical industry. The use cases were presented with reference to the PharmaLedger project [3]. The concepts of traceability and serialization were highlighted, as well as distinct use cases that represent the routine activities of the pharmaceutical industry. All these were presented under the impact of blockchain technology and they want to be concrete examples that demonstrate how blockchain technology can improve a certain industrial sector, in this case, the pharmaceutical one. As a research and technology partner who co-led with Novartis the architecture work package in an extended consortium [3], we contributed to defining the final architecture and advanced research technologies to create a trust blockchain platform in a private-public partnership between research entities and pharma companies [3]. This partnership advanced previous research results [4, 5] on decentralization through self-sovereign applications [6, 7, 8] under OpenDSU blockchain technology [9].

A. Blockchain as middleware for "trust"

Trust is relational, subjective, limited (up to a certain point), and unfolds in a certain direction and a certain context. The "trusted middleware by or for" is not a specific physical or logical location, but rather a metaphorical "place" where algorithms and data are manipulated so that the parties involved in processing the data can work together to create value without disclosing data or intellectual property (this is the case with algorithms) [10]. In fact, we can say that everything can act as a trusted middleware, but the condition is that there is a standardized environment, agreed upon between the parties.

Currently, there is no standardized, scientifically recognized form of the term "Blockchain" [11]. The legislation for adaption is still at the beginning of its development [12]. However, blockchain is a revolutionary technology [13, 14, 15] that will be predominantly used in one form or another depending on the case or the participants. Condos [16], defines blockchain as an electronic ledger for records of digital data, events, or transactions that are managed by participants in a distributed computer network.

Blockchain middleware refers to the software functions that are designed to unite different interconnected instances and elements of blockchain data. It can also encompass software to

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combine different implementations into a single interface for ease of use and (often) to achieve scalability [17]. In certain industries, blockchain middleware can be used as a replacement for current blockchain technologies. Abstracted, middleware services are universal services that serve as a link between platforms and applications [18]

As we advance in time, the infinite and limitless needs of consumers increase in quality, and their demand for food, products, and pharmaceuticals is directly proportional to the safety they provide. By the term safety, it is understood that they offer the possibility of verification, transparency, and traceability. Therefore, companies or enterprises must find solutions to adopt new technologies. One solution that is amenable to companies meeting consumer needs is blockchain technology.

To respond to business needs and to develop efficient, secure, and prosperous supply chains, the industry must identify and define these needs. The industry needs to work together to identify the intersections where interoperability is needed and to establish standards, then, with the help of innovative technologies, success can be achieved globally.

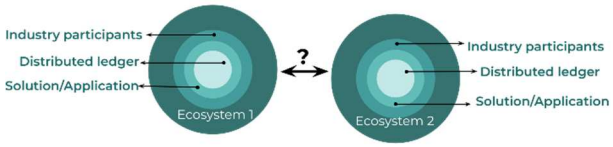

Fig. 1. Interoperability of ecosystems

Interoperability refers to the basic ability of different computer systems with different infrastructures to easily connect and communicate with each other, even if they were developed as part of different ecosystems. As can be seen in the image above (figure no. 1), to ensure traceability, members or participants of industries must come together, and collaborate, to develop process and application standards for specific business problems (depending on the industry in which they operate) that they are trying to solve. Establishing an additional layer in the blockchain that provides a level of trust and validation about event data that traditional data sharing mechanisms fail to provide results in a collaboration between participants to ensure interoperability of traceability solutions based on blockchain.

II. Blockchain In The Pharma Industry

Industry 4.0 is a global strategic initiative that aims to bring about a technological revolution in the field of industry [19]. Recently, Industry 4.0 solutions have been used in the pharmaceutical industry under the regulation of multiple stakeholders to ensure safety and protect the welfare of the entire society [20]. The pharmaceutical sector is a high-tech, knowledge-intensive, and highly regulated industry. All aspects of the life cycle of new drugs are regulated, from patent application to marketing approval, commercial exploitation, patent expiration, and competition with generic drugs [21].

Counterfeit and falsified drugs [22] can then be immediately identified and safely withdrawn from circulation. The solution to this problem has been identified with the name of serialization [23]. In this regard, to prevent counterfeiting, a prerequisite is the assignment of a unique serial number linked to the production data of the item (item identification code, expiry date, and batch number) in the form of a type barcode Data Matrix.

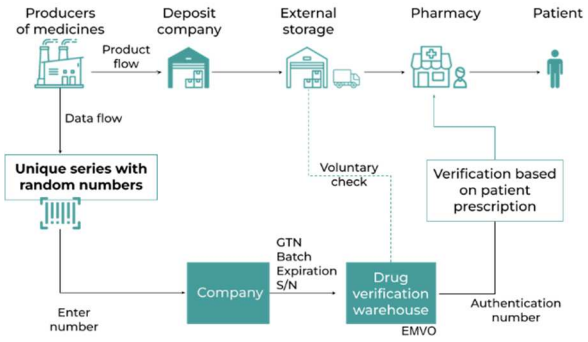

Fig. 2. Serialization and traceability of ecosystems

The safety of pharmaceutical agents and food devices is a major issue and a longstanding public concern [24]. So, traceability ensures the safety of medicines and is the basis of absolute trust on the part of the consumer, both in the pharmaceutical industry and in its products. The latter is the "key" to guaranteeing trust between participants.

A. Blockchain human-centric healthcare solutions - PharmaLedger

PharmaLedger [3] has the ambition to provide a trusted, widely used platform to support the design and adoption of blockchain-enabled healthcare solutions. To succeed, PharmaLedger will need to build trust, which in turn requires investment in strong stakeholder engagement and open communication. Validation of the PharmaLedger blockchain platform is done in three preselected Domain Reference Applications (DRA) [25]: DRA1: supply chain; DRA2: Health Data Marketplace and DRA3: Clinical Trials. DRAs were developed as blockchain-based flagship demonstrators that serve as flagship pilots to generate industry trendsetters and early adopters

eLeaflet/eProduct-Information (ePI)

The first use case, within the supply chain (DRA1), is eLeaflet/eProduct-Information (ePI). The user/consumer checks through the ePI whether the commercial item (medicine) is not counterfeit, as well as other updated information about it, regarding the validity, manufacturer, etc. Through the ePI/eLeaflet, electronic information is constantly updated.

This use case starts with the creation of ePI ("Electronic Product information") in digital form by the manufacturer, review, and approval of the ePI with the health authorities, updates of the ePI, and dissemination of the ePI to the patient/physician /provider (HCP). As mentioned above, medicines are regulated and scientifically validated. They are dispensed and prescribed to patients and consumers safe. Health professionals also inform patients and consumers about the safe use of medicines.

When we refer to ePI, we refer to electronic product information. It aims to improve and enable access to up-to-date

information about medicines. They are created and updated by manufacturers, and then reviewed and approved by health authorities. Later, after verification, they are published by the manufacturers and given access to the target audience (patients, HCP providers).

Patient access and safety are paramount. Regulatory efficiency can protect them by making the pharmaceutical industry green, in the sense that it is clean. This would also stimulate the economy in a positive sense, as counterfeiting pharmaceutical products would be avoided. As an example, Greece ranks 1st in terms of relative job losses due to the circulation of counterfeit products [26].

With the help of blockchain technology, trust, interoperability, security, and privacy can be ensured. To ensure trust, PharmaLedger [3] proposes transparent and immutable records of review and approval transactions, as well as smart contracts that establish transaction rules so that only approved eLeaflets are published.

In terms of interoperability, it facilitates transactions between manufacturer systems and healthcare authorities, with easy access for patients through the One App. It is also proposed to build more uses into the barcode to increase the digital value. For security, they propose a decentralized system and off-chain information storage for ePI to provide a secure platform instead of a central database, increasing resilience against cyber-attacks. In the case of confidentiality, they ensure data sovereignty and anonymity in a primary, non-negotiable way.

Clinical supply chain

The second use case, within the supply chain (DRA1), is called the clinical supply chain.

Companies have one-up or one-down visibility of data, which means they can see information from adjacent partners, but not the entire supply chain. Regulatory compliance across multiple legacy systems results in manual, paper-based processes that are slow and costly. Sponsors have little information about whether and how their product is being consumed, reducing the ability to improve processes. The solution, therefore, creates value for all stakeholders by building trust, increasing efficiency, and eliminating key pain points that improve the ability to get critical medicines to patients around the world.

In other words, in the second use case, trust, traceability, interoperability, and immutability are ensured at the level of patients, manufacturers, couriers, clinical sites, and health authorities. In this case, clinical sites represent the hospitals and other medical facilities that participate as clinical trial sites, clinical trial sites, and that see patients according to the protocol. Trust is enabled and created between partners by using a common platform. Increasing confidence in product qualities is achieved by all actors in the clinical supply chain. Interoperability is ensured by the allocation of interoperable data points (eg: product layout), which leads to faster decisions. PharmaLedger also offers unique access to information about sponsors and couriers from clinic staff. In the case of immutability, keeping records immutably reduces the burden of audits and inspections. Traceability improves the ability to track responsibility and reconciliation of medicines, so that product waste reduction can be ensured through true end-to-end visibility.

Traceability of finished products

The third use case, within the supply chain (DRA1), is called the traceability of finished products in the supply chain. The Pharma supply chain is complex as each node in the chain consumes and provides data from/to other nodes. The use case looks at methods of data capture and transfer, on/off-chain storage in a flexible mobile and integrative architecture that will enable reliable visibility of the downstream supply chain with the availability of real-time data. PharmaLedger connects the supply chain ecosystem for fast and reliable information exchange. Therefore, they facilitate the incorporation of new partners into the ecosystem, including patients.

Today's Pharmaceutical Industry does not have "end-to-end" visibility. Demand signals are delayed and distorted. There is also a manual reaction to withdrawals, information kept hidden, and a large number of IT interfaces. PharmaLedger proposes increased patient safety, fast and efficient withdrawals, cost optimization for the benefit of health systems, simplified IT interfaces, and unlocking the visibility of hidden information.

To increase the degree of trust, secure and timely delivery of products will be achieved with the help of digital identities. Interoperability is achieved by leveraging industry standards such as Advanced Shipping Notices (ASN) and Electronic Product Coding Information Services (EPCIS) for end-to-end traceability. Immutability enables secure and immutable information sharing for reliable demand signals and product counterfeit detection. Traceability ensures increased regulatory compliance, providing product provenance and chain of custody.

Anti-Counterfeiting

The fourth use case, within the supply chain (DRA1), is called Anti-Counterfeiting.

Multi-Factor Product Authentication (MFPA) is a publicly available smartphone application for drug users (patients or guardians) and extensible for institutional users (registered). Anti-Counterfeiting Data Collaboration (ACDC) is a virtual database that connects data from the "on/off-chain" and produces real-time analysis, alerts, reports, and information.

Trust is based on the response of the authorities, which is a reliable one regarding the authenticity of a medicine. Regarding privacy and security, anonymity is guaranteed in read-only, public access scenarios. Interoperability allows the same solution to be adopted by all manufacturers and markets without getting locked into proprietary solutions. Scalability is achieved on Leaflet/ePI and using the existing serialization rule.

DRA1 use case capabilities provide an end-to-end traceability model using blockchain, which could support upstream to downstream processes in the supply chain. The capabilities of each use case reinforce the overall impact of DRAs.

Clinical Trial Recruitment

The fifth use case, within health data (DRA2), titled Clinical Trial Recruitment, intends to create a patient-centric, industry-wide clinical trial recruitment solution. The solution would aggregate clinical trial and submission criteria across the industry, and use a matching algorithm to match the patient with relevant clinical trials.

When we refer to decentralization, this use case creates a shared permission ledger accessible by network participants without putting any party in charge. In the case of immutability, a permanent record of studies submitted by sponsors is created. This discourages any illegitimate use of the process matching infrastructure. Cross-industry records of matching attempts are shared with patients, increasing understanding of the testing criteria that may cause them to match or fail. This 4builds trust.

Personalized Medicine

The sixth use case, within health data (DRA2), is titled Personalized Medicine.

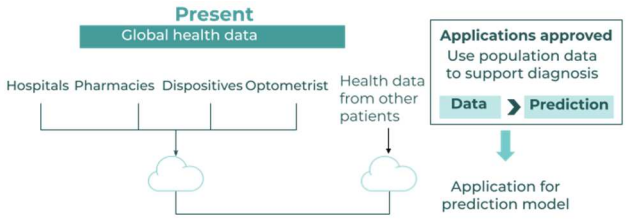

Fig. 3. Personalized medicine (currently)

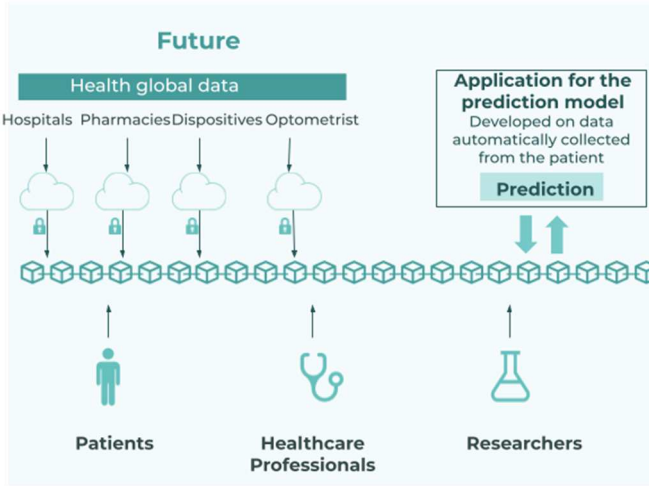

Fig. 4. Personalized medicine (future)

Currently, patients have concerns about how their data is used. Additionally, hospitals do not hold all patient information regarding all past medical records. Currently, this would be a complex, expensive, and time-consuming process (figure no.3). As can be seen in figure no. 4, the future is promising. Patients will be in control of their data and healthcare professionals will have access to historical patient health data. This data will facilitate the medical process, which will allow the prevention/elimination of certain risks or more accurate diagnosis by medical professionals. Also, patients could receive personalized and effective treatment much faster. In this sense, medical data about patients could also help researchers in their studies. The main objective is to validate the use of blockchain in combination with Machine Learning (ML) and Artificial Intelligence (AI) for the creation and application of algorithms and models that improve healthcare delivery.

The personalized medicine use case aims to establish a trusted environment that supports patient-centered solutions for generating RWE (Real-World Evidence) for research purposes and quality healthcare. These can be applied to improve diagnosis prevention and personalized treatment of patients.

Confidence in healthcare is improved through better clinical decisions, making value-based healthcare more achievable. Transparency provides a complete overview of your data. Security is represented by the privacy and security of data through the blockchain. In terms of interoperability, it improves data connectivity and reduces the lag time from providing RWD (Real-World Data).

Regarding the capabilities of the DRA2 use case, it provides a model using the blockchain that could support the identification of their traceability as well as claims in the field of health data.

eConsent

The seventh use case, within the clinical trials (DRA3), is entitled eConsent.

If a potential study participant does not feel confident, empowered, or safe when reviewing the informed consent document, the likelihood of their participation is reduced, affecting recruitment into the clinical trial.

The objective of this use case is to provide all actors in clinical trials (study participants, healthcare organizations/CRO ethics committees, suppliers, and regulatory authorities) with a blockchain-based platform for process oversight, leveraging the status of digital consent provided by study participants.

Concerning trust, audit findings will be reduced or eliminated and opportunities for fraudulent data can be reduced by increasing the consistency of information that is viewed on investigative sites. In the case of immutability, an immutable entry is created in the blockchain, recording when consent was obtained, which is immediately visible to users with appropriate permission under the General Data Protection Regulation (GDPR). Smart contracts can be implemented to block access to study systems until consent is obtained, ensuring compliance with good clinical practice (GCP).

Medical IoT Devices

The eighth use case, from clinical trials (DRA3), is entitled Medical IoT Devices.

Connected health devices or networked IoT medical devices and Remote Patient Monitoring (RPM) technologies can provide quality data to support patient medical records. This use case aims to validate and test blockchain technology for the dynamic acquisition and processing of data from medical devices assigned to patients to be monitored for heart failure in a pediatric observational clinical trial.

Trust is ensured by sharing reliable and verifiable data, anchoring the blockchain. Security is guaranteed with an IoT security framework, through information based on DIDs (decentralized identities). The acquisition and dynamic processing of data from the consumer to the medical devices are achieved with the help of smart contracts to accelerate the development of the clinic. Privacy is achieved through continuous and/or discrete remote measurement and patient trajectory in clinical trials.

Regarding the capabilities of the DRA3 use case, it provides a model using blockchain that could support investigator identification and Point of Care (PoC), to submission and payments in clinical trials.

The selected use cases compose a vision of how they can together support a value chain to generate impact, for and across DRAs (across the pharmaceutical value chain).

III. Insights and Research Results

PharmaLedger project's main goal is to transform a research project into a Digital Trust Ecosystem. The first step in this direction was to research the proper architecture [27] and a three layers platform architecture emerged. On top of the networking layer which connects the blockchain domain's nodes (replicas), there is an "on-chain" layer with consensus-building methods and an "off-chain" layer containing the health data containerized under an innovative concept called DSU (Data Sharing Units) and pioneered in the OpenDSU [5] open-source framework. The proposed storage capabilities are ensuring that the scalability and confidentiality of the solution built over the PharmaLedger platform get fulfilled. The backend OpenDSU APIHub is another particularity of the architecture while DSUs should be understood as a ledger (technically a microledger) that can store immutable data, distributed to a limited group of stakeholders. The chosen strategy to implement microledger is the Self-Validating Data technology, a generic approach for implementing the idea of having a ledger for every DSU.

Once the architecture and technologies to be used were agreed upon, the first implementation challenge was integrating the APIHub with the Quorum blockchain. The major observed challenges in trying to implement the proposed solution were the transaction's low speed, the Corporate Policies regarding security and deployment, and the throughput since Quorum blockchain scalability [28] is limited to a few hundred transactions per second.

During the project the original OpenDSU architecture suffered improvements to mitigate the challenges, allowing two types of executions, optimistic and direct ones. In this sense, in some situations smart contract methods can be executed in an "optimistic" way, which does not require the consensus algorithm validation since the anchoring commands could be implemented in a "self-consistent way", significantly reducing the time of response for the human users' commands. This approach can be extended to the anchoring process continuing to increase the performance and scalability of the blockchain. Treating blockchain anchors as SVDs, allows anchors to have blockchain-like properties (non-repudiation, immutability, and traceability) while still being stored off-chain. The provenance of data is trustable due to blockchain immutability, SVD states in general, and OpenDSU anchors in particular. The overall openDSU proposed solution to anchor the data into the blockchain and not store it on-chain offers better performance.

Three important strategies were identified for anchoring and depending on the problems, different ledgers and implementation strategies of ledgers can be chosen, offering blockchain agnosticism and multi-blockchain technology support for the platform.

Other challenges encountered involved the deployment of the blockchain platform where it was identified the need to separate the deployment for APIHub from the blockchain node which would communicate via HTTPS to eliminate any non-compliance security concerns.

Privacy issues and risks which involve the protection of personal data, of patients in particular were analyzed and treated individually by use case. Specific mitigation measures were proposed as anonymization and in special Differential Privacy, DSU storage approach, and Verifiable Credentials to add a supplementary layer of trust in data provenance.

We recommend the usage of Enclaves [29] and Cloud Vaults [30] for Keys storage (hardware storage when possible). To ensure anonymized personal information and anonymized health-data there were developed privacy-by-design techniques. OpenDSU technology facilitates developers to create complex applications by reducing the hurdles of handling cryptographic keys or complex blockchain technology stacks.

The Enclave concept appeared in OpenDSU under the influence of the pharma industry culture and regulations which accelerated the understanding and enhancement of Security Contexts. All the results are internally documented within PharmaLedger deliverables and improvements regarding the technology are accessible in the open-source documentation [31].

IV. Conclusions

The integration of digital technologies in the health sector promises to make healthcare safer, better, more personalized, and generally more efficient [32]. In the First Report of Engagement of Regulatory and Standardization Strategy [33], PharmaLedger sets out and documents a plan for the regulatory and standardization approach and strategy.

To inspire trust with stakeholders, it is of paramount importance that PharmaLedger builds effective relationships with them. At the same time, stakeholders should also be classified and subdivided into the following groups: decision-makers/regulatory bodies, standardization bodies, patients, industry, organizations working with blockchain technology, and other stakeholders (including research centers).

National and European decision-makers and regulators have a direct impact on the implementation and success of the PharmaLedger solution, supporting the project in navigating the regulatory landscape and other barriers. Standardization bodies can influence standardization work in all industries. The involvement of PharmaLedger in standardization processes is an essential part of the architectural development of the PharmaLedger platform, as existing standards should be properly implemented to support the interoperability of the platform. The involvement of patients and patient organizations should be encouraged with the greatest possible care, as patient participation in healthcare has been associated with improved treatment outcomes [34]. Industry associations such as the European Federation of Pharmaceutical Industry Associations (EFPIA), European Hospital and Healthcare Federation (HOPE), European Medicines Verification Organization (EMVO), and Medicines for Europe (MfE) are also important in contributing to engagement activities stakeholders and in facilitating participation in standardization bodies [33]. PharmaLedger also wants to explore opportunities to collaborate with other organizations involved in blockchain technology, such as the BC Observatory, the Horizon 2020 MHMD project, and the American PhUSE project [33]. At the same time, research centers are particularly essential for

obtaining information, sharing knowledge, and continuous learning.

An effective regulatory engagement strategy requires a focus on ensuring that all stakeholder engagements are managed in a logical, transparent, and well-coordinated manner by defining how regulatory relationships and communications will be managed at the project level [33]. This creates standardized practices, processes, and tools that can help build successful relationships with regulators. The ambition of the project is to build a strategic approach to interactions and, where possible, to combine or strengthen various interactions.

The project intends to build a better understanding of its role in the development of digital health and to build public trust by trying to be an example of transparency by engaging with regulatory authorities and publishing clear information. PharmaLedger will welcome and actively seek feedback from external regulatory and standards bodies [33]. The project will include them at an early stage to be as inclusive as possible and to invite their views where the project's use cases need input to move forward. However, regulatory activity [33] can also unlock new opportunities when it encourages investment, increases legal certainty, adapts applicable rules to specific situations, and standardizes complicated procedures. Through successful interactions with regulatory authorities, it is possible to positively influence the outcome of the mentioned activities, adapt the outcome to the goals of PharmaLedger, and create new opportunities. PharmaLedger [33] will work collaboratively and strategically with regulators, both EU and US, to facilitate the sharing of findings and support the drive towards more effective digital health. The approach to this first level of engagement will be through round tables with groups of experts and decision-makers. Therefore, a well-established and effective engagement between PharmaLedger and the regulatory authorities increases the chances of success of the proposed solutions.

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