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CDMO: Ever-growing market share

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FROM THE EDITOR

CDMOS FACE CHALLENGES

CDMOs are benefiting from a solid market environment. Projects to bring complex biological products to market, sophisticated delivery systems and changes to the regulatory framework in the pharmaceutical industry all favour the growth of the subcontracting market.

The majority of the emerging biopharmaceutical companies and a growing number of pharmaceutical firms are entrusting their development operations to CDMOs, because new drug development activities require the mobilization of a diverse and ever-increasing range of competencies. Due to the costs involved, it has become impossible for one pharmaceutical firm to set up and keep multidisciplinary teams of high-level experts working exclusively on a single project. Spreading these costs across several projects enables CDMOs to provide the levels of expertise required for each project. By accumulating the experience gained on several projects, CDMOs can provide the competencies required to take on increasingly complex projects.

Over the last two years, the biggest CDMOs have made very expensive acquisitions to enable the roll-out of clinical trial, development and manufacturing services for cell and gene therapies, with the aim of offering their clients a complete supply chain – from development activities through to the production stages of the most sophisticated, high-value-added forms.

However, the practice of organizing CDMOs around Centres of Excellence responsible for supplying world markets could be undermined by the trade wars between major powers, and other Brexit-type events. The supply chain organizations established to date could be called into question and replaced by new strategies of relocation as close as possible to markets.

Competition between CDMOs has started a race to make strategic acquisitions of target companies possessing specialized expertise in high-value-added forms and an industrial organizational structure capable of supplying local markets. These target firms are quite rare birds on the market and their values in EBITDA multiples could soar.

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BLOCKCHAIN: HOPES & CHALLENGES

What is the reality of blockchain in the pharmaceutical industry? The tangible repercussions of blockchain, i.e. the decentralized ledger system copied and stored on multiple nodes across the networks, now go far beyond the Bitcoin (the cryptocurrency that gave rise to it) and are increasingly impacting all spheres of the economy.

By Cécile Théard-Jallu and Victor Fabre

Thanks to the enhanced transparency, security, traceability, efficiency, speed of transactions and reduced costs that it generates, many industry leaders have already achieved significant business benefits. The blockchain phenomenon has already started growing in the pharmaceutical industry through various R&D initiatives. However, blockchain also comes with technical and legal challenges that shall be primarily addressed as a condition to its development.

A DEVELOPING PRESENCE IN THE PHARMACEUTICAL INDUSTRY

The core principle of blockchain is to set up a distributed ledger system, made of "blocks" of verifiable transactions. The ledger is encrypted throughout the chain, each transaction being checkable through its previous and subsequent transaction (getting rid of trusted third-parties who are traditionally entrenched in society, such as banks, insurers or internet platforms...). The purpose is to prevent a single user from controlling the transaction data: the data stored becomes resistant to corruption as the various nodes that constitute the information form a consensus to determine if the data is legitimate and thus authorized. In that sense, the blockchain structure is unique, as it is formed by a series of hash values, where the hash value of the previous block is included in the current block.

Among a series of advantages of blockchain, the first obvious ones are security & immutability. Whereas most common databases can be easily hacked (because of their centralized features), the blockchain technology guarantees the integrity of the data processed.

Contrary to a traditional repository system with limited access, blockchain can also work as a single platform, but interoperable between the different actors. In this respect, blockchain goes beyond "one-up

and one-down model, where information is passed only between adjacent trading partners".[1] Blockchain could comprehensively process all data through the process (for instance in the drugs supply chain or clinical trials) and deliver secured information to the intermediaries.

The third clear benefit is transparency as blockchain provides a greater visibility on the flows of drugs consumed or distributed.[2]

Based on these characteristics, the blockchain technology responds particularly well to the pharmaceutical industry's core needs for drugs track-and-trace, origin certification and supply chain governance. Blockchain is therefore actively explored through proof-of-concept initiatives that have triggered notable interest among a number of pharmaceutical actors.

CHECKING THE AUTHENTICITY OF RETURNED PRODUCTS AND STREAMLINING THE SUPPLY CHAIN

Verifying the returned drugs can constitute a first concrete use case. Due to excessive stock piling at the wholesaler level, the pharmaceutical laboratory may wish to resell those products (representing billions of dollars of sales every year). A blockchain, that any relevant player may interrogate, will help verify the authenticity of the products through their serialization numbers and manage product stocks by confirming whether a drug is available for resale.

Since February 2019, the EU has set up a central repository linked to EU Member States' national serialization databases[3], which players may interrogate to check such authenticity. However, other countries, such as the US, do not offer this centralized approach. For those other countries, a blockchain may serve as a common database gathering manufacturing data and which manufacturers and distributors could interrogate to check products' availability.

For instance, in 2017, Merck in collaboration with SAP started the development of a first SAP Pharma Blockchain POC application[4] for this case of use (the app also offering a geographical localization feature to help locate the products and their transfers from one actor to another).

Tracking & tracing drugs need to be ensured throughout the supply chain, including by having industrial actors communicate their manufacturing data about the drugs. At their level, logistics, transportation and dispensation actors need to check drugs through handling, transportation and storage stages. A blockchain can streamline this whole process by allowing any participant in the supply chain to ensure that logistics and transportation guidelines of the drug manufacturer (humidity, temperature, air quality, storage, manipulation, etc.) are being strictly followed. Huge amounts of data are generated through this process and need to be shared to ensure its efficiency and security. However databases can be scattered and blockchain constitutes a suitable tool to reinforce and facilitate compliance & governance within the supply chain. Smart contracts (those computer protocols that facilitate, verify and execute the negotiation or execution of a contract), possibly operating in the scope of a blockchain, may serve to identify potential breaches and adapt storage conditions so as to avoid excessive

Idea in Brief

Opportunities. The impact of blockchain now goes far beyond the Bitcoin. And the healthcare industry will not be spared by this technological wave as blockchain features, i.e. its security and immutability, distributed form and transparency, are ideally suited to address the core-needs as well as the challenges faced by this industry.

Growing use. That is why we have been witnessing a growing use of blockchain in this industry, for instance by supporting serialization which enables track and trace of the supply chain of drugs, or by securing clinical trials and in particular how patient consents to participate therein.

Challenges. Yet, major obstacles may be seen as persisting in the implementation of blockchain and shall be solved. Among those challenges are technical feasibility, the environmental impact of blockchain under certain circumstances of use and development, and, last but not least, the legal challenges that users will need to face including data privacy compliance issues or greater liability risks.

1 www.pharmaceuticalonline.com/doc/is-blockchain-the-solution-to-drug-traceability-0001

2 http://23consulting.com/wp-content/uploads/2018/07/SUPPLY-CHAIN-REPORT-VF.pdf

3 See our previous articles in PHARMANetWork on serialization of drugs in the EU: "Where do we stand in the serialization process as the February 9, 2019 deadline gets closer? " n°39 page 56, "Update on the serialization process in Europe" no. 36 page 56, "Serialization in Europe: a decisive step about to be taken" no. 29 - page 48, These three articles can be viewed online on the PHARMAnetwork magazine website www.pharmanetwork.digital

4 https://blogs.sap.com/2018/04/17/blockchain-co-innovaion-in-the-pharmaceutical-industry/ www.ledgerinsights.com/saps-pharmaceutical-blockchain-goes-live/

energy consumption resulting from unnecessary storage.

SECURING CLINICAL TRIALS

Blockchain may help increase security in how patient consents to participate in a clinical trial are obtained and stored, hence also increasing the quality of the clinical trial results.

Informed consent of the patient implies that the patient is informed of each step of the trial process including related risks. Consent to the trial protocol and its possible updates must be transparent for the patient and traceable for healthcare actors. However, in practice, this process is hard to control and formalism is not always complied with, if not fraudulent in some cases. This may impair the reliability of the trial results, and as a consequence, the placement of the product on the market.

Blockchain may help bring traceability and transparency throughout the process, for instance by time stamping consent forms and transforming them into forgery-proof documents. Additional smart contracts may be set up in connection with any update of the trial protocol requiring patient renewed consent.

Beyond patient recruitment, a blockchain may be looked at to help store and manage the data either by the healthcare practitioners or the patients themselves. For instance, this is what the EXOCHAIN blockchain project purports to do.[5]

ANOTHER EMBLEMATIC USE CASE IS THE FIGHT AGAINST DRUG COUNTERFEITING

Since drug companies manufacture and deliver innumerable medicines, keeping track of all those products is an arduous task. That has unfortunately led counterfeiting activities to flourish posing serious threat to both patients and industrial actors, with this threat being even higher in developing countries.[6]

Counterfeit medicine often occurs when the product packaging or its labelling information contains a false representation in relation to its identity or source.[7] And, most of the time, the pharmacist, the healthcare provider or final user cannot, or are not trained enough to, detect this false representation.

Blockchain has a solution for this as well: as drugs move across the supply chain, the transactions together with the identification of related drugs, can be recorded in a blockchain, thereby providing a distributed ledger right from the time of its origin. This will enable all parties to track drugs through the entire supply chain life cycle from the original source of the products. Novartis is among those having led a PoC of blockchain aiming at answering those functionalities.

Of course, this will need to cope with applicable legislations, including in the EU with the Falsified Medicine Directive adopted in 2011 by EU Member States and which became enforceable on February 9, 2019. This legislation aims at harmonizing measures in the EU to fight against medicine falsifications, in particular by adopting obligatory safety features such as serialization, i.e. a "unique identifier and an anti-tampering device" to be displayed on drug packaging.[8]

Serialization basically works as a comprehensive system serving to track and trace the supply chain of drugs from manufacturing to dispensation to the patient.[9] Serialization functions through the affixation by the drug manufacturer of a unique serial number, in addition to the batch number. With this serial number, each stakeholder manipulating the medicine product will be able to verify the authenticity of the product by interrogating the official

5 https://exochain.com/

6 According to recent OECD statistics, about 10% of pharmaceutical products sold are counterfeits (Safeguarding against substandard/counterfeit drugs: mitigating a macroeconomic pandemic. Wertheimer AI, Norris J Res Social Adm Pharm. 2009 Mar; 5(1):4-16.)

7 www.ncbi.nlm.nih.gov/pmc/articles/PMC3617666/

8 https://ec.europa.eu/health/human-use/falsified_medicines_en.

9 www.pharmamanufacturing.com/articles/2015/serialization-drug-quality-security-act/

repository base. At the end of drug's life cycle, the pharmacist or the hospital will simply deactivate the serial number.

It appears from the characteristics of the project that blockchain could be used as a supportive technology to help the traceability function of serialization.

As mentioned above but this time in the fight against drug counterfeiting, blockchain systems could enable the pharmaceutical industry to share their serial numbers on the blockchain - decentralized and distributed with timestamps - where wholesalers, dispensaries, and prescribers would access to verify the provenance of the drug. A series of projects already work around this feature, for instance the French IT publisher Adents in collaboration with Microsoft.[10]

BEYOND THE PROMISES, A SERIES OF CHALLENGES REMAINS TO BE SOLVED

Yet, the implementation of blockchain in the pharmaceutical industry also carries its own hurdles.

The most salient challenge posed by blockchain is the **enormous volume of data** that it needs to digest in order to operate. Indeed, billions of new drug products enter the market every year and this gigantic volume to deal with is exacerbated by the distributed feature of blockchain where every information is automatically duplicated among all the nodes. This increases the storing of datasets in a substantial way. Yet, experts note that "blockchains do not scale well when it comes to high volume transactions."[11]

This leads to the second issue, i.e. the **environmental impact of the blockchain technology**. The distributed feature is indeed a security guarantee but it can also be, depending on the context of its use, a great energy-guzzler. Let's remember that the energy consumption of bitcoin has been reported as consuming at its peak more electricity than 159 countries.[12] Smart contracts designed to better manage energy consumption are good tools to help solve this issue but the task remains huge.

Finding a **relevant business model** may also be an issue for blockchain actors (how to finance, how to value, how to protect and who should own the intangible assets linked to the blockchain technology while it is shared and distributed in many nodes...).

Legal obstacles will also be encountered in the implementation of blockchain. Indeed, **when it comes to blockchain, existing regulations** may be unfit to support it.

Among various topics, we may first undoubtedly find the **privacy aspect.** Blockchain may lead to the collection and and processing of personal data, and therefore will fall under the scope of the now famous EU General Data Protection Regulation (also known as the "GDPR"), with its stringent compliance rules and high standards of protection. GDPR rules are likely to conflict with some of blockchain's basic functionalities. For instance, blockchain technology makes it extremely difficult to modify the information stocked in it. Once the dataset is stood, then the distributed feature of blockchain prevents any alteration of this dataset. This might conflict with the GDPR rights conferred to the data subject, especially the right to erasure of personal data. One will also need to identify who is the data controller or joint controllers or even the data processor(s) if any and the articulation between all actors.

While it is being used in a clinical context, blockchain is also very likely to collect and process sensitive data, like health data relating to the data subject. GDPR provides for tightened controls and rules when the data controller happens to collect and process such sensitive data as the risks for the rights and freedom of the data subject are

10 https://adents.com/release-adents-microsoft-introduce-blockchain-serialization-solution-supply-chain-security-3654.html
11 https://hackernoon.com/databases-and-blockchains-the-difference-is-in-their-purpose-and-design-56ba6335778b
12 https://digiconomist.net/bitcoin-energy-consumption

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higher. As a result, the processing is in itself prohibited unless falling within a number of exceptions. National EU Member States legislations may bring in even tighter rules (e.g. French law). Last but not least, processing data through the blockchain potentially means transferring personal data outside the EU. This is subject to specific legal guarantees (the transfer is prohibited by the GDPR unless complying with a number of conditions or falling within a series of pre-authorized transfers: to adequately protecting third countries, using standard contractual clauses, binding corporate rules etc.). However, blockchain is designed as a distributed database where nodes are located anywhere.

It is worth noting that the French data protection authority (the "CNIL") has tried to provide guidelines for the setting up of blockchain consortium, letting the feasibility of blockchain as an open discussion regarding the right to be forgotten, to have one's data modified or to object to the processing, while technologies still need to be evaluated in their conformity with the GDPR.[13] The EU is also studying how to implement this technology in the most efficient and legally secured manner.[14] Some projects have for their purpose to find solutions for the enhancement of data privacy in blockchain (see for instance the Substra project"[15]).

Another legal challenge is liability. The risk for a patient is material and can be systemic if for instance transactions or traceability are not settled correctly. And so is the risk for security and confidentiality of the data. The lack of monitoring on the platform could be sufficient to trigger the liability of the company. As the technology is still difficult to master, the question of the allocation, nature and degrees of liabilities cannot be ignored, especially during the negotiation of agreements.

A third topic is how to validly prove the existence of and modifications brought to transactions, with the possibility to access, store and share them. For instance, under article 1366 of the French Civil Code, proof of a legal act requires that its author may be duly identified. This would logically require the presence of a trusted third-party to confirm the link between the act and the author thereof. Yet, blockchain's principle is to eradicate trusted third-parties... Additionally, blockchain is likely to evolve in an international environment raising the need to cope with a variety of legal regimes possibly contradicting each other. In this same international background, the question will be **which law to choose to govern the blockchain activities and which court shall have jurisdiction** in case of a conflict.

Blockchain naturally also comes with the concept of **cryptocurrencies**, which may benefit the blockchain members (see for instance the development of ICOs -or Initial Coin Offerings- allowing a company to levy funds in cryptocurrencies instead of traditional money). Beyond the new flexibility offered, these cryptocurrencies will possibly not be eligible for any guarantee on the part of the State if the blockchain's activities cease and the holder loses the value of his bonds, contrary to currencies issued by a Sovereign State, which may come with a guarantee to indemnify the bond's holder if the bank goes bankrupt.

Those topics are among those needing to be explored and it is clear that stakeholders should answer them all when intending to engage into a blockchain project. In the field experimentation, with the support of regulatory actors, will also be key to blockchain's success in the pharmaceutical industry. ■

13 www.cnil.fr/en/blockchain-and-gdpr-solutions-responsible-use-blockchain-context-personal-data
14 https://ec.europa.eu/digital-single-market/en/blockchain-technologies
15 www.aphp.fr/contenu/owkin-lance-le-projet-collaboratif-substra-pour-liberer-le-plein-potentiel-de-lia-dans-la