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REVIEW

# Blockchain technology for advanced therapy medicinal products: Applications in tracking, data sharing, and supply chain automation

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**Abstract:** Advanced therapy medicinal products (ATMPs) like cell and gene therapies offer transformative treatment options for many diseases. However, coordinating the decentralized, patient-specific manufacturing of autologous ATMPs across multiple hospitals poses major supply chain challenges. This paper provides a comprehensive analysis of how blockchain technology can enhance decentralized ATMP manufacturing networks. First, background on ATMPs and complexities of decentralized production is reviewed. An overview of blockchain architecture, key attributes, and existing use cases then follows. The major opportunities for blockchain integration in ATMP manufacturing are discussed in depth, including tracking autologous products across locations, enabling data sharing between hospitals to power AI-based optimization, automating supply chain processes, and maintaining provenance records. Critical limitations around scalability, privacy, regulation, and adoption barriers are examined. Design considerations for developing blockchain ecosystems tailored to the unique ATMP environment are also explored. Blockchain shows immense promise for transforming visibility, coordination, automation, and data unification in decentralized ATMP manufacturing networks. Despite current challenges, blockchain is prepared to profoundly impact the advancement of personalized cell and gene therapies through enhanced supply chain instrumentation. This paper provides a comprehensive analysis of this emerging technological innovation and its applications to address critical needs in ATMP translation and manufacturing.

**Keywords:** blockchain, advanced therapy medicinal products (ATMPs), artificial intelligence (AI), cell and gene therapies, GMP facilities

# 1 Introduction

Advanced therapy medicinal products (ATMPs) such as cell and gene therapies represent groundbreaking new treatment options for many diseases like cancer, genetic disorders, and autoimmune conditions. These novel treatments modify a patient's genes or cells to treat their medical condition. However, the customized nature of many autologous or allogenic ATMPs, using the patient's own cells or donor's cells, poses challenges for decentralized manufacturing across networks of hospitals and academic facilities. Tracking each individualized cell or gene therapy product through decentralized production networks is crucial yet difficult with conventional supply chain systems. Additionally, aggregating and sharing manufacturing data spread across multiple sites is key to optimizing and standardizing processes. Emerging blockchain technologies offer promising solutions to address these ATMP manufacturing challenges through enhanced supply chain transparency, data sharing, and process automation.

This paper provides a comprehensive analysis of blockchain technology and its potential applications in advanced therapy medicinal product manufacturing. First, the background of ATMPs and the complexities of coordinated decentralized manufacturing are outlined. An overview of blockchain architecture, key characteristics, and existing use cases then follows. Next, the major opportunities for blockchain integration in ATMP production are discussed in depth. Critical challenges and limitations that must be considered are also examined. Design considerations for developing blockchain models tailored to ATMP environments are then explored. Finally, the outlook and future trajectory of blockchain in revolutionizing supply chain and data management for ATMPs are considered.

## 1.1 Bridging distinct disciplines for groundbreaking solutions

This work resides at a pioneering intersection of blockchain technology and ATMP manufacturing, addressing a crucial gap not widely explored in current literature or practice. The novelty of our approach lies in the interdisciplinary fusion, leveraging the capabilities of blockchain to improve complex and personalized ATMP production processes. This synthesis presents a transformative paradigm for ATMP manufacturing, monitoring, and regulatory compliance, marked by greater efficiency, reliability, and patient safety. Our contribution is significant as it establishes a framework for integrating cutting-edge technology in biomedicine, thereby streamlining the path from the laboratory to the patient. By analyzing the complexities of this integration, our analysis reveals a new horizon in personalized medicine, emphasized by blockchain's promise of immutable traceability and decentralized operation.

## 1.2 Background on ATMPs

ATMPs include gene therapies, somatic cell therapies, and tissue engineered products. These novel biologics utilize genetic modification or human cell and tissue engineering to treat debilitating diseases with significant unmet needs. Gene therapies introduce, alter, or silence targeted genes to correct genetic defects or alter disease pathways. Somatic cell therapies involve administration of human cells like T-cells or stem cells to regenerate damaged tissue or fight cancers or autoimmune disorders. Tissue engineered products use cells seeded on biocompatible scaffolds to regenerate or replace damaged organs and tissues.

The European Medicines Agency (EMA) classifies ATMPs as biological medicines that undergo substantial manipulation to alter their function or structure or isolating specific cell subpopulations. This substantial manipulation during manufacturing, alongside ethical and safety considerations, necessitates stricter oversight under the EMA's ATMP regulations compared to other biologics. However, the transformative therapeutic potential of ATMPs make developing manufacturing and supply chain capabilities to deliver these novel treatments to patients imperative [1,2]. Many ATMPs use autologous cells, derived from the patient's own body, which are genetically modified or engineered *ex vivo* into therapeutic agents administered back to the same patient. This autologous nature adds major complexity compared to traditional biologics produced in large batches. Each patient-specific product must be individually manufactured, tracked, and delivered, essentially constituting a batch size of one. The need to coordinate personalized manufacturing across multiple hospital sites provides motivation for innovative solutions to enhance supply chain orchestration. Thus, the customized and personalized nature of many academic ATMPs poses major difficulties for traditional centralized manufacturing models. Each patient-specific product must complete a complex sequence of delicate process steps involving cell collection, viral vector production, genetic modifications, cell expansion and formulation. However, no single facility inside of academic circuit may have all the specialized expertise, cleanrooms, and equipment needed across this value chain. This requires coordinating production across multiple hospital nodes in a decentralized manufacturing network. Tracking the identity and chain-of-custody for each autologous or allogeneic product across various facilities is extremely challenging with conventional supply chains. Additionally, aggregating distributed datasets from diverse organizations to identify optimize operating parameters through AI is difficult due to data isolate silos. Overall, these decentralized, patient-specific production networks create immense coordination, transparency, and data sharing challenges unmatched by traditional biologics manufacturing, specially within healthcare institutions. Therefore, there is a clear need for innovative digital solutions to coordinate academic ATMP manufacturing across networks of facilities while maintaining the stringent regulatory compliance.

## 1.3 Decentralized ATMP manufacturing networks

Hospital-based Good Manufacturing Practices (GMP) facilities enable bench-to-bedside translation of ATMPs by bridging research, manufacturing, and clinical application within the same institution. However, the infrastructure and regulatory requirements make establishing in-house GMP production capabilities difficult, especially for smaller academic hospitals and research centres [3]. This has driven formation of manufacturing networks which coordinate development and distribution of ATMPs across multiple nodes.

In decentralized models, various centres possess specialized expertise like cell collection, vector production, or cell expansion and formulation. The personalized cell or gene therapy products move between sites undergoing sequentially required manufacturing processes based on each node's capabilities. This distributed model avoids replicating capabilities at each location. However, the growing network complexity stresses conventional supply chains. Materials, inventories, expiration dates, bio-process data, funds, assets, and products must flow ordered between heterogeneous nodes to achieve the best process outcome and prevent delays that could compromise personalized product quality or patient outcomes. A major priority is tracking and coordinating each patient-specific autologous or allogenic product's identity, manufacturing history, and chain-of-custody throughout the various production stages across locations. Conventional linear supply chains with fragmented data systems cannot provide the real-time transparency, tracking, and coordination essential for personalized ATMP networks. Blockchain has emerged as a promising technological innovation capable of profoundly enhancing decentralized ATMP supply chain orchestration and data unification.

# 2 Overview of blockchain technology

Blockchain is a distributed digital ledger technology initially developed to serve as the immutable decentralized ledger for cryptocurrency transactions. The ledger consists of concatenated blocks of transactions or data. Each block contains a cryptographic hash of the previous block, creating an immutable chronological chain where altering any data corrupts the chain [4].

Distributed consensus algorithms validate each transaction, with copies of the ledger synchronized across multiple nodes in a peer-to-peer network. This decentralized architecture seeks to avoid dependency on any central authority or node which minimizes the vulnerability of the system. Cryptography-based identities and permissions control access and roles like reading or writing data. Key characteristics of blockchain include as follows:

(1) Decentralization: Distributed across networks of peer nodes rather than been centrally controlled. In a decentralized system, control and decision-making are distributed across a network of independent nodes, rather than concentrated in a unique or central authority. This means that no entity ever has complete control over the entire network. This feature improves system resilience and reduces risks associated with central points of failure or vulnerability, such as in centralized systems.

(2) Transparency: All participants share the same single version of the truth. This means that the visibility of transactions and activities is available for all network participants at the same time. Each participant has access to the same ledger, which records all transactions. This 'unique version of the truth' ensures that all participants can see the same data and verify transaction history, promoting trust and accountability.

(3) Immutability: Cryptography makes transactions nearly impossible to alter. Once a transaction is recorded on a blockchain, it cannot be modified or deleted. This is achieved through the use of cryptographic hashing and the blockchain structure, where each block is linked to the previous one. Modifying any transaction would require changing all subsequent blocks in each node, which is computationally infeasible in a decentralized network. This property is crucial to ensure data integrity and reliability.

(4) Security: Cryptography & permissions provide network and data access controls. Blockchain technology uses advanced cryptography to protect data transactions. Cryptography not only ensures the immutability of the records but also helps secure the network. Additionally, blockchain networks typically have permission access, meaning that not just anyone can join the network or view its content. This layered security approach helps to protect sensitive data and finally the network from unauthorized access and obviously from cyber-attacks.

(5) Consensus: This feature is based on the necessary rules for validating transactions across distributed nodes. In a distributed network, consensus mechanisms are used to agree on the validity of transactions. Since there is no central authority dictating what is valid, network nodes follow a set of rules, named 'consensus algorithms' to agree on the state of the ledger. This process ensures that all valid transactions are democratically agreed upon by the network and are recorded consistently across all copies of the ledger.

(6) Provenance: Provides complete traceability for all the products and assets. This ability to trace the history and origin of an item or asset permits in the blockchain, every transaction or movement of an asset is recorded, creating a permanent historical record. This feature is particularly valuable in supply chain management as it allows products to be tracked from their origin at every step of their journey, ensuring authenticity and compliance.

Each of these features plays a crucial role in the unique advantages that blockchain technology can offer, including greater security, greater transparency, and greater efficiency in various applications extending initially just from financial transactions to supply chain management including those that are involved in the ATMP process. These attributes (Table 1), make blockchain highly attractive for supply chain and manufacturing applications needing real-time transparency, robust traceability, and data integrity across multiple parties. Public blockchains like Ethereum [5] allow open participation while private or hybrid models restrict access to closed ecosystems like supply chain consortiums. A growing multitude of pilot projects are exploring blockchain applications across pharmaceutical value chains. One example is MediLedger [6], a blockchain system sponsored by pharmaceutical industry leaders and the FDA to prevent fictitious entering supply chains. It provides real-time monitoring such as drugs moving between companies. Another is Modum [7, 8], which uses Internet-of-Things temperature sensors and blockchain to enable continuous monitoring and logging of environmental conditions during shipments. Overall, blockchain is gaining traction as its capabilities for supply chain root, coordination, and data sharing become more recognized. Building on these developments, additional initiatives are underway to further leverage the potential of blockchain in the pharmaceutical industry. For example, projects like PharmaChain [9], focus on improving drug traceability and authentication. This system uses blockchain to record every step of a medicine's journey from manufacturing to the end user, ensuring authenticity and compliance with regulations. There is also growing interest in using blockchain to manage clinical trial data. By ensuring data integrity and secure sharing of trial results, blockchain can play a crucial role in improving trust and efficiency in clinical research. As blockchain technology continues to evolve, its applications in the pharmaceutical sector are expected to expand, offering promising solutions to long-standing challenges such as counterfeiting, human errors, supply chain inefficiencies and finally regulatory compliance [8].

**Table 1** Blockchain attributes and healthcare benefits

| Blockchain Attribute | Definition | Benefits for Healthcare |
|---|---|---|
| Decentralization | Distributed ledger across peer-to-peer network, no central authority | Avoid single point of failure, enhanced resilience |
| Transparency | All participants share same ledger transaction history | Improved auditability, aids regulatory compliance |
| Immutability | Cryptography makes transactions very hard to alter | Data integrity, tamper-resistance |
| Security | Cryptography and access controls limit data access | Protects sensitive patient information |
| Consensus | Rules for transaction validation across nodes | Democratic agreement on state of ledger |
| Provenance | Full traceability of asset/data source and history | Improved supply chain visibility, product authenticity |

# 3 Opportunities for blockchain integration in ATMP manufacturing

The third generation of blockchain technology, often referred to as blockchain 3.0, has expanded beyond its initial focus primarily on financial applications. It has evolved to address non-financial use cases in other industries, making blockchain a versatile, general-purpose technology. These applications cover a variety of areas such as identity management, legal dispute resolution, contract management, supply chain management, insurance, and healthcare. Figure 1 is a process representation and relationships within "Blockchain-Driven Data Integration for Academic ATMP Manufacturing in Enhancing Healthcare Collaboration and AI Optimization." Explains how blockchain technology enables the secure, efficient sharing of data between a variety of stakeholders: hospitals, academic institutions, and various research groups. This integration allows major sources of data to be exchanged seamlessly so that critical information can be shared, leading to greater collaboration, and to help with the application of its AI and manufacturers processes of healthcare. The network is critical, showing the potential ATMP development and application, emphasizing the sharing of data in a way that streamlines; an ecosystem to foster academic research and the move toward personalized medicine.

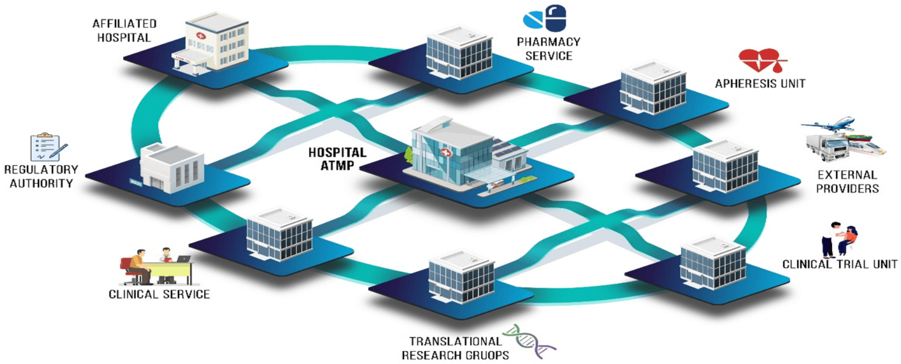


**Figure 1** Blockchain-driven data integration for academic ATMP manufacturing in enhancing healthcare collaboration and AI optimization

Healthcare, in particular, has become a really important area to explore the potential of blockchain. Numerous use cases have been identified in the healthcare field. However, due to the relative newness of blockchain and the prevalence of no justified speculation, it is essential to obtain accurate information and knowledge about its usefulness and future in the healthcare industry. Researchers and practitioners seek to understand specific application areas, the development of blockchain-based healthcare applications, the challenges and limitations these applications face, ongoing efforts to address these challenges, and opportunities for improvement [10, 11].

The features and emerging applications indicate blockchain's strong potential to address imperative needs in advanced therapy medicinal product manufacturing:

## 3.1 Track and trace of autologous cell therapies across decentralized networks

A predominant priority with decentralized ATMP production is maintaining identity and chain-of-custody for each personalized patient's product as it moves through upstream and downstream operations at different nodes. It's a fact that conventional linear supply chains lack real-time visibility and rely on fragmented tracking records, usually depending on manual entry, across different locations that require them to be centrally organized, and potentially vulnerable. This impedes traceability once issues arise, or delays occur during the distribution of fragile living cell products with limited stability or limited expiration dates.

Blockchain ledgers provide continuous end-to-end tracking as ATMP material and product shipments enter each node. Sensors could monitor environmental conditions during transport while location tags provide oversight throughout processing steps within each facility. Thus, each manufacturing milestone, logistical move, and quality check gets immutably logged on the blockchain ledger with timestamps and digital signatures. This creates complete chronological documentation of the product's journey, facilitating rapid identification of any deviations from normative or regulation timeframes that could flag potential problems needing intervention. Whether anomalies arise, the historical trail facilitates a traceability footprint root for the investigation.

The transparency across all stakeholders enables real-time coordination and scheduling. This represents a notorious advance in manufacturing rate. Thus, production planning adapts to unpredictable variability in manufacturing timelines for each autologous or allogenic batch. Nodes only proceed once upstream release and distribution milestones are verified, preventing delays or complications from compounded errors. Patients also benefit from enhanced oversight minimizing risks of compromised product identity, integrity, or clinical outcomes.

### 3.1.1 Use case: Enhancing cell therapy product tracking with blockchain

A critical challenge in decentralized ATMP manufacturing is ensuring the integrity and traceability of cell therapy products as they traverse through various production stages across different facilities. A blockchain-based solution can revolutionize this process by creating an immutable, end-to-end traceability system. For instance, imagine a blockchain platform designed specifically for cell therapy manufacturing, akin to a hypothetical project, "CellChain." In this system, each step of the cell therapy product's journey—from cell collection, processing, and expansion to the final delivery to the patient—is recorded on a blockchain. This not only ensures traceability but also significantly enhances the transparency and reliability of the manufacturing process. A practical example of this concept in action is the collaboration between T-cell therapy developers and blockchain startups to implement a pilot project. This project aims to tag each batch of cells with a unique digital identifier that is recorded on the blockchain at each step, providing a real-time, tamper-proof record of the product's journey.

A concern dilemma for decentralized ATMP production networks is to unify isolated data distributed across diverse organizations into accessible knowledge to optimize and standardize the processes. Although manufacturing steps occur at different nodes, the therapy product and source material are linked end-to-end to the value chain. Analyzing relationships between processing factors, clinical indications, bioprocess results and therapeutic outcomes could require aggregating heterogeneous datasets from multiple and distant sources or nodes. Safety and efficacy rely on consistency between individualized batches and require comprehensive analysis only possible by combining datasets that otherwise remain disconnected.

In this regard, Blockchain offers a mechanism to incentivize and orchestrate the controlled exchange of data between nodes necessary for more powerful and accurate AI modelling. The ledger structure allows entries from various activities, such as patient sample testing, vector characterization, efficiency of viral transduction, cell expansion data, or clinical results, to be recorded cumulatively in an immutable chronological sequence with the provenance of the data recorded explicitly.

Smart contracts automate conditional data sharing, releasing particular inputs once defined conditions are met. For instance, manufacturing data could be automatically recorded after quality controls are passed [12, 13].

In the field of blockchain technology, a smart contract is a pivotal innovation, representing a blend of legal framework and digital automation. Proposed initially in the 1990s, smart contracts are essentially code-based protocols integrated in a blockchain, designed to autonomously execute all the predefined contractual terms. These digital contracts serve as self-operating tools, executing actions when certain conditions are fulfilled. They eliminate the need for intermediaries, thereby streamlining transactions. Functionally, smart contracts are related to the well-known and automated "if-then" statements; upon meeting specific criteria, they execute related actions, such as record updates. Smart contracts ensure transactional integrity and immutability, as once executed, the records on the blockchain cannot be altered in any way. This characteristic introduces a new level of security and transparency in transactions, particularly relevant in fields requiring meticulous documentation and compliance, such as the pharma and GMP regulations [14].

These blockchain-encoded data sets can then drive advanced AI algorithms to discover optimized production parameters and material specifications needed to achieve target clinical criteria. Transparency builds institutional trust and confidence that sharing data on blockchain will mutually benefit all stakeholders through improved processes and patient outcomes. Cryptography and permissions controls also provide critical safeguards for sensitive data sets. Overall, blockchain makes it easy to create comprehensive data sets from fragmented sources necessary to unlock the power of AI for next-generation ATMP manufacturing [15].

#### 3.1.2 Hypothetical scenario: Decentralized data aggregation for AI optimization

ATMP manufacturing involves a plethora of data, from patient-specific genetic information to bioprocessing parameters. Currently, this data is siloed within different institutions, hindering the optimization of manufacturing processes through AI. A blockchain-based system, "GenoBlock," could facilitate the secure and efficient sharing of genetic and bioprocessing data across different nodes within the ATMP manufacturing network. By leveraging smart contracts, GenoBlock could automatically authorize the sharing of data once predefined conditions are met, such as the successful completion of quality control checks. This shared data pool could then feed into AI algorithms to identify patterns and optimizations, significantly improving the efficiency and efficacy of ATMP production.

#### 3.1.3 Automating and enhancing supply chain processes

Indeed, Blockchain's programmable smart contracts allow automating time-consuming manual processes like tracking purchase orders, inventory, expiration date, product releases, auditing, and other documentation workflows essential for GMP compliance in ATMP production. Internet-of-Things sensors also integrate with blockchain networks for functions like environmental monitoring, access control, and location tagging [14]. Smart contracts, integral to data science and AI, offer scalable solutions to handle large data sets, enhancing trust, integrity, and access control. The integration of AI with smart contracts in blockchain technology offers significant enhancements in terms of validation, security, and functionality. AI can be used to validate smart contracts, and various AI algorithms, including deep learning principles like Tensor, can be integrated into the contracts themselves. This integration is exemplified in the research by Sun and Gu [16], who developed a machine learning method specifically for the rapid and efficient detection of vulnerabilities in blockchain-based smart contracts. This approach is not only fast but also highly effective, making it an ideal prefilter to increase traditional symbolic analysis methods. This integration of machine learning into blockchain vulnerability detection intend a significant step forward in enhancing the accuracy and speed of identifying potential security issues within smart contracts.

Blockchain technology from its origin as the technology behind bitcoin has evolved to become a crucial component in various industries, thanks to its decentralized and reliable system. This is particularly evident in the field of cognitive computing, a specialized branch of AI that mimics human cognitive processes in digital environments. Cognitive computing exploits data analytics and machine learning to not only enhance human-machine interactions but also to significantly boost the capabilities of smart contracts. By integrating human-like thought processes and execution constraints, this AI subset shines in improving the accuracy of smart contracts, enhancing traditional AI methods. It notably enhances aspects such as data transparency, access control decentralized, and confidence derived from blockchain-based smart contracts. Furthermore, the application of cognitive computing in healthcare, highlighted in a survey by Daniel et al., emphasizes the critical importance of adhering to regulatory standards, demonstrating its potential to transform blockchain applications in the medical field [17].

Federated learning, a concept aligning with blockchain's decentralization ethos, offers a distributed and collaborative learning approach [18]. It allows for the management of data access without centralizing raw data, which is particularly relevant for sensitive and widely dispersed types of data like healthcare information including for instance in clinical trials. The synergy between smart contracts and federated learning facilitates innovative research opportunities. Lu et al. [19], demonstrated this fact by proposing a privacy preservation strategy for the industrial Internet of Things, integrating federated learning into blockchain consensus to optimize data processing and address limitations in computational infrastructure. This strategy highlights the need for data privacy and addresses unresolved issues related to limited computing resources.

Building on this, recent advances in the field have further explored the integration of federated learning with blockchain, particularly in the context of healthcare data management. The novel approach, called FLchain [20], as clarified in recent studies, combines the decentralized aspect of blockchain with federated learning to create a more secure and efficient system for data processing and analysis. In this model, each participating node in the network contributes to the learning process, while the blockchain framework ensures data integrity and privacy. This methodology is especially relevant in scenarios where data cannot be centralized due to privacy and data protection concerns including logistical limitations, such as in the case of patient data in clinical trials. Furthermore, the implementation of FLchain in healthcare is revolutionizing clinical research. Through facilitating the secure exchange of patient data between multiple institutions while maintaining individual privacy, federated learning within a blockchain framework enables a more comprehensive and collaborative approach to medical research. It allows a larger data set to be analyzed without direct data transfer, thus ensuring compliance with stringent data privacy laws and ethical standards. Additionally, the use of smart contracts in this integrated approach automates various processes within the healthcare data management system. For instance, allowing access to data for research purposes once patient consent is verified. This automation not only improves efficiency but also plays a crucial role in maintaining fidelity and compliance with the data management process. Thus, the fusion of federated learning with blockchain technology, as demonstrated by recent research, presents a revolutionary solution for managing complex and sensitive data in various fields, particularly in healthcare. It offers a novel way to address the challenges of data privacy and complying with general data protection regulation, resource limitations while raising collaborative and innovative research opportunities. "As this technology continues to evolve, it has the potential to significantly impact how data-driven decisions are made in healthcare and beyond." [18, 21].

#### 3.1.4 Example: Smart contracts for streamlined supply chain management

The management of supply chain processes in ATMP manufacturing, from tracking inventory to ensuring compliance with GMP regulations, is highly complex and manual. Blockchain technology, through the use of smart contracts, can automate these processes, reducing human error and increasing efficiency. For instance, the "SmartGMP" blockchain project could automate the release of cell therapy products based on real-time inventory and quality control data. If a product passes all quality checks, a smart contract is triggered to update the inventory and notify the downstream facility, preparing it for the next phase of production. This automation streamlines the supply chain, ensures regulatory compliance, and reduces the time to deliver therapies to patients.

## 4 Challenges and limitations of blockchain technology

While blockchain offers tremendous potential to transform ATMP manufacturing, limitations and challenges exist that must be carefully considered:

### 4.1 Scalability

The scalability of blockchain technology is a critical concern, particularly in the context of public blockchains. Basically, public blockchains rely on computationally intensive consensus algorithms, such as proof-of-work, to validate transactions. In a proof-of-work system, the participants (called miners) compete with each other to solve complex mathematical problems.

The first miner to solve that problem gets the right to add a new block of transactions into the blockchain. This process requires significant computational effort and energy, therefore the term "proof of work." The principal purpose of proof-of-work is to prevent fraudulent transactions and ensure the integrity and security of the blockchain. These mechanisms ensure security but limit transaction processing performance. The Bitcoin blockchain processes 7 transactions per second, while Ethereum handles between 15 and 30 Supply chain applications need to handle thousands of transactions to track material flows. Private blockchains avoid this by restricting participation, allowing for optimized consensus and higher performance. However, the data storage remains a limitation. Public chains store all chain data on the ledger, which limits scalability as the chain grows. Private blockchains can keep data off-chain and store only hash links on the chain to improve scalability. However, this reduces transparency as the data is not fully visible. Hybrid architectures and layered solutions such as sidechains are active areas of blockchain scaling research and represent ongoing efforts to address these scalability challenges.

## 4.2 Interoperability

Another major hurdle is the integration of blockchain technology with existing supply chain systems. Most supply chains use a combination of enterprise resource planning (ERP), manufacturing execution system (MES), laboratory information management system (LIMS), and other on-premises systems [22–24]. Integrating various hospital information systems with each other. Additionally, emerging blockchain platforms, are a challenge. The lack of mature open standards requires reliance on custom integrations, creating fragile and complex interfaces between these kinds of evolving systems. This means that open standards are still maturing, so interoperability currently depends on customized integrations. However, maintaining complex interfaces between on-premises, cloud, and rapidly evolving blockchain systems is fragile and corruptible. Major technology providers now offer blockchain solutions as a service on cloud platforms to accelerate adoption by reducing integration barriers.

## 4.3 Data privacy and security

Blockchain's inherent transparency poses unique challenges in handling sensitive patient information and general data protection regulation. By default, blockchains provide transparency environment where all participants are able to see data. Regarding to patient information, visibility must be restricted only to authorized clinical users. Solutions such as private channels where data is partitioned to subsets of participants provide one solution. However, data outside the blockchain in secondary storage like IPFS (decentralized file system) and HDFS (distributed file system) must also be encrypted [25]. While blockchain is conceptually resistant to any hacking, vulnerabilities in smart contract code, cryptographic keys, or wallets persist and all of them require rigorous cybersecurity plan. Most enterprise blockchains are hosted on-premises or private cloud rather than public blockchains with the objective of limiting exposure and minimizing security risks.

## 4.4 Lack of standards

Blockchain remains an emerging technology with many competing platform options and a lack of dominant standards and well-established. This makes platforms riskier due to vendor or creator lock-in fears. Leading technology firms and open-source groups are collaborating to develop interoperability standards. The IEEE (Institute of Electrical and Electronics Engineers) (https://www.ieee.org/), has standards projects focused on blockchain integration and security while the Enterprise Ethereum Alliance publishes specifications for enterprise Ethereum capabilities. The development of open-source standards will increase blockchain adoption by reducing switching costs between platforms when required [26, 27].

## 4.5 Unclear regulatory guidelines

The regulatory landscape for clinical blockchain implementations remains uncertain. Thus, regulatory uncertainty around clinical blockchain implementations poses challenges. Decentralized autonomous organizations that enforce rules via smart contracts do not align well with traditional regulatory models for manufacturing oversight. The 21st Century Cures Act directs the FDA to support innovation around digital healthcare, including blockchain to improve data sharing and integrity [28]. The FDA has demonstrated an openness to blockchain but has not yet issued formal guidance, due to the robustness of the technology, it must be done in a short period. Communicating benefits around safety and transparency will be key to driving forward policy evolution to support blockchain integration.

# 5 Blockchain design considerations for ATMP environments

Implementing blockchain solutions for ATMP networks requires optimizing designs for the unique needs of biopharmaceutical environments:

## 5.1 Permissioned *vs* public blockchains

Public blockchains allow anonymous participation and maintain highly decentralized consensus mechanisms like proof-of-work mining. The choice between public and permissioned blockchains is essential. However, as we mentioned above, open anonymity faces an intense and clear conflict with general data protection regulation and clinical data privacy requirements for authorities and verified identities, controlled access, and audit logs. In contrast, permissioned blockchains restrict participation to authorized and well-known entities and use consensus models like Istanbul BFT that optimize for throughput over extreme decentralization. Permissioned blockchains remain distributed across all the manufacturing nodes but avoid the risks of public anonymity, and offer a tailored solution to the data privacy challenges. These systems restrict access exclusively to a consortium of known, authorized participants, significantly reducing the risks associated with anonymous interactions. Permissioned blockchains, such as those built on Hyperledger Fabric, adopt consensus models like Istanbul BFT [29], which prioritize throughput and efficiency over extreme decentralization, aligning more closely with the needs of regulated industries. The architecture of Hyperledger Fabric shows a novel approach called execute-order-validate. This modular architecture breaks down the transaction process into three separate phases, enormously improving flexibility and scalability. In this framework: (i) Execution (Endorsement): Transactions are proposed and then executed by designated endorsers without updating the ledger. This process ensures that only valid transactions, complying with predefined endorsement policies, proceed further. (ii) Ordering: Transactions are sequenced in a block, without regard to their content, ensuring consistency across the network without revealing confidential details to all participants. (iii) Validation: The ordered transactions are validated against the ledger's current state and endorsement policies. Invalid transactions are discarded, ensuring integrity and consistency. This architecture addresses the inherent disadvantages of public blockchains by enabling controlled access and maintaining privacy, crucial for applications beyond cryptocurrencies. The execute-order-validate model ensures that transactions are processed efficiently, securely, and in compliance with the necessary regulatory standards, making permissioned blockchains like Fabric an ideal choice for industries with stringent security and privacy requirements [10]. (Table 2)

**Table 2** Comparison between permissioned *vs.* public blockchains

| Feature | Permissioned Blockchains | Public Blockchains |
|---|---|---|
| Access Control | Restricted to authorized entities | Open to anyone anonymously |
| Consensus Model | Models like Istanbul BFT, optimizing for throughput | Decentralized mechanisms like proof-of-work |
| Data Privacy | Tailored solutions for data privacy, controlled access | Risks due to public anonymity |
| Scalability and Efficiency | Higher, due to controlled access and optimized consensus models | Lower, due to extensive decentralization |
| Regulatory Compliance | More suitable for regulated industries | Faces challenges with data protection regulations |
| Architecture | Utilizes an execute-order-validate model for enhanced flexibility- -and scalability | Traditional, less flexible models |

## 5.2 On-Chain *vs* off-chain data storage

Balancing transparency with scalability is crucial when deciding data storage methodologies [13]. Determining optimal data storage design is crucial when developing blockchain solutions for ATMP manufacturing. This decision requires balancing the competing priorities of transparency and scalability in decentralized supply chain ecosystems. On-chain storage, with all data written directly into blockchain transaction blocks, best incorporates blockchain's ethos of transparency and immutability. Every batch, process parameter, logistical milestone, and clinical outcome can be permanently recorded to create an immutable audit trail for enhanced supply chain visibility. However, storing entire datasets on-chain severely limits scalability and throughput as the blockchain grows exponentially over the product's useful lifecycles. Contrary, the off-chain storage in external encrypted repositories relieves the blockchain while improving flexibility at the same time. Bulk data sets like manufacturing metrics or genetic sequences are stored in decentralized file systems like IPFS or private databases. The strategy is that only hash pointers get stored on-chain to verify integrity without enlarging the ledger size.

However, this interesting strategy based on data compartmentalization is clearly in conflict with the transparency spirit of blockchain and can obstruct supply chain analysis. Hybrid models attempt to balance both priorities following regulatory guidelines. Critical manufacturing records and clinical data necessary for patient safety and oversight transparency remains stored on-chain. Bulk genomic data files, real-time bioprocess values, and Internet-of-Things sensor streams are received into an off-chain data pool for accessibility while only hashes append to the blockchain. Compute-intensive analytics, like personalized AI optimization, tap both external data pools and on-chain metadata. This layered design facilitates strict standards-compliant data transparency while still streamlining performance for scalability. Tailoring storage topology across on and off-chain resources to meet regulatory obligations allows blockchain projects to balance decentralization with practical efficiency needed for clinical translation. Reviewing prototypes with partners using no-identified datasets also promotes optimum architectures for supply chain integration. Overall the differenced strategy promises improved visibility while ensuring data privacy patient safety remains the highest priority [25]. However regulatory guidelines may require retaining raw data on-chain. The use of data pools alongside blockchain may balance these competing demands between transparency and scalability (Table 3).

**Table 3** Comparison between on-chain *vs.* off-chain data storage

| Feature | On-Chain Storage | Off-Chain Storage |
|---|---|---|
| Transparency and Immutability | High, as all data is permanently recorded on the blockchain | Lower, data stored outside the blockchain |
| Scalability | Limited, as storing complete datasets reduces throughput | Higher, as it relieves the blockchain from bulk data |
| Data Accessibility | Direct and permanent record on the blockchain | Accessed via hash pointers, not directly stored on-chain |
| Suitability | Best for critical data requiring transparency and auditability | Suitable for bulk data, enhancing flexibility and efficiency |

## 5.3 Identity and access management

Implementing fine-grained access policies enforced through public-private key cryptography is essential for privacy and confidentiality across diverse ATMP network participants. Stringent identity, personal data, and access management represents a pivotal priority when developing blockchain ecosystems for ATMPs across decentralized manufacturing networks. Participants span diverse roles from logistics providers to biotechnologists, to quality engineers to physicians with very varying data visibility requirements. However, the inherent transparency of blockchains seemingly conflicts with restricting access to confidential data. Multi-layer cryptography-based permissions provide solutions tailored to ATMP contexts requiring compliance and patient privacy alongside supply chain transparency. Public and private key infrastructure underpins user identity verification on the blockchain, facilitating an auditable authentication. Smart contracts then dynamically administer access policies enabling need-to-know data isolation. For example, ATMP's manufacturing operators can scan material inventory on-chain meanwhile the manufacturing methods remain hidden from external logistics partners. At the same time for instance testing facilities insert quality release certificates without exposure to protected health and private information from clinical teams. Thus, the role-based and attribute-based access control mechanisms implemented in solidity code restrict data fields. Zero-knowledge proof algorithms also facilitate encryption allowing verified queries without fully decrypting documents. So, this cutting-edge technology that allows the verification of information without revealing it while adding a high level of security and privacy. Thus, this defense-in-depth approach encapsulates regulatory principles of privacy-by-design while retaining blockchain's benefits of immutable centralized documentation. The cryptography can seem computationally intensive but Permissioned architectures optimize performance for healthcare environments. Since the fact that patient outcomes are involved, dedicating resources to ensure ethical oversight, general data protection regulation, and compliance establishes trust in decentralized clinical innovation. Access policies will co-evolve with institutional learning and regulatory guidance. But rationalizing identity on blockchain networks promises to balance transparency with confidentiality imperatives across ATMP development pipelines needing accountability [21].

## 5.4 Integration with internet-of-things and digital twins

Improving supply chain visibility in ATMP manufacturing requires the integration of Internet-of-Things technologies. Incorporating environmental sensors, equipment monitors, and location tags via Internet-of-Things integration layers allows far greater upstream and downstream supply chain profiles. Digital twins mirroring the physical flows of logistics and inventory provide simulation and optimization capabilities. The combining blockchain, Internet-of-Things, and digital twins enables both real-time tracking and digital modelling for process improvements. Decentralized manufacturing networks for personalized advanced therapies involve numerous geographically distant facilities coordinating complex logistics. Tracking each autologous or allogeneic batch through this web of operations poses immense supply chain challenges. Conventional linear systems lack real-time downstream and upstream visibility across locations needing tight coordination for personalized biologics with limited stability. However, combining blockchain ledgers, Internet-of-Things devices, and digital twin architectures establishes a cyber-physical instrumentation backbone tailored for personalized medicine supply chains. Blockchain delivers an immutable sequenced record of manufacturing milestones, logistical moves, and clinical administration. Internet-of-Things sensors embedded at critical infrastructure points feed quantified environmental and equipment data into blockchain for monitoring product conditions. Digital twins mirror biological, clinical, and operational flows to model variability through analytics and simulations. This solid fusion provides unprecedented supply chain transparency, adaptability, and optimization capabilities. The chronological blockchain ledger continuously tracks custody transfers between facilities as smart contracts automate data exchange upon batch release. The location tags and condition monitors provide oversight for delicate living therapeutics while warning of deviations. Digital twins assess uncertainties or gaps and guide contingency plans. The integrated technological trio overcomes the limitations of individual solutions usually found in traditional commercial options. Blockchain coordinates decentralized operations, Internet-of-Things captures metrics for decision augmentation, and digital twins dynamically advise responses using AI-based heuristics. Together, they enable resilient orchestration of personalized production despite unavoidable variability in biological source material and clinical outcomes. Supply chain leaders emphasize that this cyber-physical digitization marks a seminal turning point for next-generation advanced therapies [23]. Figure 2 shows the integration and adaptation of blockchain technology and AI in healthcare, particularly in the manufacturing of ATMPs, address several critical challenges and propose innovative solutions.

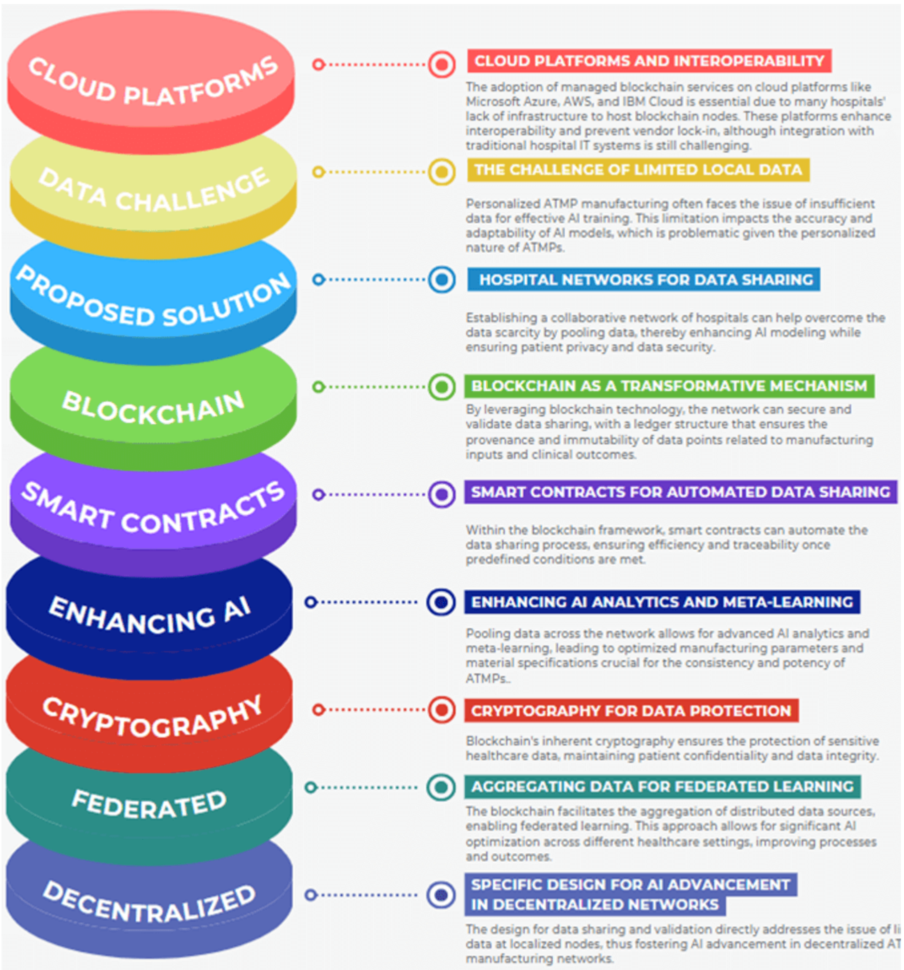


**Figure 2** Blockchain integration in the manufacturing of ATMPs in the healthcare system

### 5.5 Cloud platforms and interoperability

Since, many hospitals lack the infrastructure to host blockchain nodes. Managed blockchain services on cloud platforms like Microsoft Azure, AWS, and IBM Cloud allow easier adoption. Major cloud providers offer interoperability between their blockchain services to prevent vendor lock-in. However, bridging with non-cloud-based hospital IT systems remains challenging. Emerging open protocols like Hyperledger Grid which connects Permissioned and public chains. Overcoming the data limitations that currently hinder AI-based optimization in the manufacturing of ATMPs the key points can be elaborated as follows:

(1) The Challenge of Limited Local Data: In personalized ATMP manufacturing, each node (or manufacturing site) often has insufficient data batches to train machine learning algorithms effectively. This limitation leads to reduced accuracy and adaptability in AI models, which is a significant challenge given the personalized nature of ATMPs [16].

(2) Proposed Solution - Hospital Networks for Data Sharing: To address this challenge, it's possible establishment of a network of hospitals or regional healthcare system. These hospitals would collaborate and securely share data, thereby collectively enlarging the datasets available for AI modelling. This network would ensure not only the enhancement of AI's effectiveness but also the protection of patient privacy, which is crucial in healthcare [11].

(3) Blockchain as a Transformative Mechanism: Blockchain technology is suggested as a key element for secure and validated data sharing between the nodes in this network. Its ledger structure allows for the cumulative logging of various manufacturing inputs (like cell characterization, process parameters, and clinical outcomes) in an immutable sequence. This ensures that the provenance of each data point is explicitly recorded [19].

(4) Smart Contracts for Automated Data Sharing: Smart contracts within the blockchain can automate the sharing of data once certain predefined conditions are met. This feature adds an extra layer of traceability and efficiency in the data-sharing process [14].

(5) Enhancing AI Analytics and Meta-Learning: By pooling data across the network into blockchain datasets, advanced AI analytics and meta-learning become possible. This approach allows for the discovery of optimized operating parameters and material specifications, essential for achieving therapeutic potency and consistency, especially given the heterogeneous nature of starting materials in ATMP manufacturing [17, 18].

(6) Cryptography for Data Protection: The inherent cryptography in blockchain networks plays a crucial role in protecting sensitive data. This is particularly important in healthcare, where patient data privacy is paramount [21].

(7) Aggregating Data for Federated Learning: Blockchain's ability to aggregate distributed, fragmented data sources into a unified knowledge base is a cornerstone for powering next-generation federated learning. This learning model is crucial for AI optimization, enhancing processes, and outcomes across various healthcare institutions [19].

(8) Specific Design for AI Advancement in Decentralized Networks: The mechanism for validated data sharing is specifically tailored to address the core issue of insufficient localized data that impedes AI advancement in individual ATMP manufacturing nodes.

## 6 Conclusion and future outlook

In summary, blockchain technology offers immense promise to address pressing needs for transparency, provenance, coordination, and data unification in decentralized advanced therapy medicinal product manufacturing networks. However, realizing benefits involves substantial integration and adoption challenges. Significant testing is still required to validate performance and optimize designs tailored for healthcare environments. Industry collaboration will be pivotal to establishing open standards and best practices.

However, the vast therapeutic and economic potential of advanced therapies warrants investment to overcome these obstacles. Transforming the transparency, security, automation, and intelligence of expanding decentralized manufacturing ecosystems could radically accelerate the promise of personalized medicines. Early successes like demonstrating blockchain's ability to unify datasets across hospitals to enhance AI modelling could catalyze rapid expansion. Although adoption is still very early, momentum is rapidly accelerating.

Many experts predict blockchain will ultimately revolutionize supply chain visibility and trust across industries through enhanced transparency, accountability, and multi-party collaboration.

For advanced therapy production, improved oversight, coordination, and optimization could result in higher-quality products, more resilient processes, and reduced costs. But most importantly for patients, clinical outcomes and access will be improved by blockchain capabilities that help manage personalized manufacturing complexity. Initial use cases to demonstrate for stakeholders the benefits of driving supply chain integration, data unification, compliance, and automation will be crucial for blockchain and ATMPs to reach their full potential.

# Conflicts of interest

The authors declare that they have no conflict of interest.

# References

[1] European Parliament C of the EU. EC Regulation 1394/2007. 2007, 64(13): 140–156.

[2] Therapies A. Reflection paper on classification of advanced therapy medicinal products Reflection paper on classification of Advanced Therapy Medicinal Products Table of contents. Therapy. 2012, 44: 1–19.

[3] European Commission. Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. European Commission Journal. 2017, 4: 1–32.

[4] Nakamoto S, System APEC. Bitcoin: A Peer-to-Peer Electronic Cash System. 2008: 1–9.

[5] Buterin V. Ethereum: A Next-Generation Smart Contract and Decentralized Application Platform. Whitepaper. 2014, 3(37): 1–36.

[6] Hang L, Choi E, Kim DH. A novel EMR integrity management based on a medical blockchain platform in hospital. Electronics. 2019, 8(4): 467.
https://doi.org/10.3390/electronics8040467

[7] Dössegger S, Peltenburg T. Next Generation Supply Chain Automation and Intelligence. Modum. 2018. (version 1.1).

[8] Bocek T, Rodrigues BB, Strasser T, et al. Blockchains everywhere – a use-case of blockchains in the pharma supply-chain. 2017 IFIP/IEEE Symposium on Integrated Network and Service Management (IM). Published online May 2017.
https://doi.org/10.23919/inm.2017.7987376

[9] Gomasta SS, Dhali A, Tahlil T, et al. PharmaChain: Blockchain-based drug supply chain provenance verification system. Heliyon. 2023, 9(7): e17957.
https://doi.org/10.1016/j.heliyon.2023.e17957

[10] Androulaki E, Barger A, Bortnikov V, et al. Hyperledger fabric. Proceedings of the Thirteenth EuroSys Conference. Published online April 23, 2018.
https://doi.org/10.1145/3190508.3190538

[11] Agbo CC, Mahmoud QH, Eklund JM. Blockchain Technology in Healthcare: A Systematic Review. Healthcare. 2019, 7(2): 56.
https://doi.org/10.3390/healthcare7020056

[12] Moosavi J, Naeni LM, Fathollahi-Fard AM, et al. Blockchain in supply chain management: a review, bibliometric, and network analysis. Environmental Science and Pollution Research. Published online February 27, 2021.
https://doi.org/10.1007/s11356-021-13094-3

[13] Swan M. Blockchain: Blueprint for a new economy. O'Reilly Media, Inc.; 2015.

[14] Taherdoost H. Smart Contracts in Blockchain Technology: A Critical Review. Information. 2023, 14(2): 117.
https://doi.org/10.3390/info14020117

[15] Aguilar-Gallardo C, Bonora-Centelles A. Integrating Artificial Intelligence for Academic Advanced Therapy Medicinal Products: Challenges and Opportunities. Applied Sciences. 2024, 14(3): 1303.
https://doi.org/10.3390/app14031303

[16] Sun Y, Gu L. Attention-based Machine Learning Model for Smart Contract Vulnerability Detection. Journal of Physics: Conference Series. 2021, 1820(1): 012004.
https://doi.org/10.1088/1742-6596/1820/1/012004

[17] Daniel J, Sargolzaei A, Abdelghani M, et al. Blockchain Technology, Cognitive Computing, and Healthcare Innovations. Journal of Advances in Information Technology. Published online 2017: 194-198.
https://doi.org/10.12720/jait.8.3.194-198

[18] Nguyen DC, Ding M, Pham QV, et al. Federated Learning Meets Blockchain in Edge Computing: Opportunities and Challenges. IEEE Internet of Things Journal. 2021, 8(16): 12806-12825.
https://doi.org/10.1109/jiot.2021.3072611

[19] Lu Y, Huang X, Dai Y, et al. Blockchain and Federated Learning for Privacy-Preserved Data Sharing in Industrial IoT. IEEE Transactions on Industrial Informatics. 2020, 16(6): 4177-4186.
https://doi.org/10.1109/tii.2019.2942190

[20] Bao X, Su C, Xiong Y, et al. FLChain: A Blockchain for Auditable Federated Learning with Trust and Incentive. 2019 5th International Conference on Big Data Computing and Communications (BIGCOM). Published online August 2019.
https://doi.org/10.1109/bigcom.2019.00030

[21] Mishra KN, Bhattacharjee V, Saket S, et al. Security provisions in smart edge computing devices using blockchain and machine learning algorithms: a novel approach. Cluster Computing. 2022, 27(1): 27-52.
https://doi.org/10.1007/s10586-022-03813-x

[22] Miao Z, Zhao G. Impacts of Digital Information Management Systems on Green Transformation of Manufacturing Enterprises. International Journal of Environmental Research and Public Health. 2023, 20(3): 1840.
https://doi.org/10.3390/ijerph20031840

[23] Mantravadi S, Møller C. An Overview of Next-generation Manufacturing Execution Systems: How important is MES for Industry 4.0? Procedia Manufacturing. 2019, 30: 588-595.
https://doi.org/10.1016/j.promfg.2019.02.083

[24] Oluwole OG, Oosterwyk C, Anderson D, et al. The Implementation of Laboratory Information Management System in Multi-Site Genetics Study in Africa: The Challenges and Up-Scaling Opportunities. Journal of Molecular Pathology. 2022, 3(4): 262-272.
https://doi.org/10.3390/jmp3040022

[25] Dhulavvagol PM, Totad SG. Performance Enhancement of Distributed System Using HDFS Federation and Sharding. Procedia Computer Science. 2023, 218: 2830-2841.
https://doi.org/10.1016/j.procs.2023.01.254

[26] Jnr. BA, Sylva W, Watat JK, Misra S. A Framework for Standardization of Distributed Ledger Technologies for Interoperable Data Integration and Alignment in Sustainable Smart Cities. Journal of the Knowledge Economy. Published online October 31, 2023.
https://doi.org/10.1007/s13132-023-01554-9

[27] Consumer I, Society T, Committee S, Projects S, Requests PA. Standards Projects. 2022: 1–50.

[28] Francis S. Collins. Testimony on the Implementation of the 21st Century Cures Act: Progress and the Path Forward for Medical Innovation — National Institutes of Health (NIH). Nih [Internet]. 2017: 1–14.
https://www.nih.gov

[29] Moniz H. The Istanbul BFT Consensus Algorithm. 2020: 1–24.
https://arxiv.org/abs/2002.03613