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"Three-Dimensional Printing in Pharmaceutical Manufacturing: Ensuring Data Integrity through ALCOA+ Principles and Regulatory Compliance"

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ABSTRACT

Three-dimensional printing (3DP) or additive manufacturing is transforming pharmaceutical sciences by on-demand production of customized drug products. The technology provides patient-specific dosing, intricate geometries, and multiple drug combinations simultaneously, presenting solutions to special therapeutic needs populations. This review assesses the existing 3DP technologies relevant in pharmaceutical production and detects the data integrity, quality control, and regulatory compliance challenges. Most important to successful integration of 3DP in medicine is compliance with ALCOA+ principles to guarantee accuracy, traceability, and security of manufacturing and digital data. High-risk concerns like file tampering, firmware hacking, and version discrepancies are addressed along with solutions such as block chain, electronic batch records, and process monitoring systems. Risk assessment tools and regulatory guidelines (e.g., 21 CFR Part 11, EudraLex Annex 11) are addressed. The article summarizes that although 3DP facilitates never-before-seen tailoring as well as decentralization, its safe use in pharmacy application requires strong data management, guaranteed documentation systems, and quality controls integrated from design to finished product.

INTRODUCTION

Three-dimensional printing (3DP), commonly referred to as additive manufacturing (AM), is a rapidly evolving technology that constructs objects by depositing material layer by layer, guided by computer-aided design (CAD) files. Initially introduced by Charles Hull in 1986, 3DP has gained considerable attention across multiple industries, including aerospace, automotive, biomedical, and more recently, pharmaceutical sciences. The core appeal of 3DP in the pharmaceutical field lies in its potential to transform conventional drug manufacturing by enabling personalized medicine producing patient-specific dosage forms in real-time, close to the point of care [1,2]. This technology facilitates the fabrication of dosage forms with precise and complex geometries, offering unprecedented flexibility in customizing the dosage strength, shape, size, colour, flavour, and drug release profile of medications. Such personalization is especially beneficial for patients with specific therapeutic needs, such as paediatrics, geriatrics, and individuals with rare diseases. The process also opens up possibilities for poly pharmacy management, where multiple drugs can be incorporated into a single poly pill with tailored release kinetics. Moreover, 3DP allows for the manufacturing of drugs in both small and large batches, making it highly suitable for on-demand, decentralized production in hospital pharmacies, clinics, or even at the patient's home using compact, customized 3D printers that utilize drug-loaded printable "inks" composed of active pharmaceutical ingredients (APIs) and excipients [3]. Multiple 3D printing technologies exist, including fused deposition modelling (FDM), powder bed fusion, inkjet printing, binder jetting, and stereo lithography (SLA). However, due to the stringent requirements of pharmaceutical products such as thermal sensitivity, dosage accuracy, and biocompatibility only a few of these techniques are currently applicable in drug manufacturing. Notably, in 2015, Spritam® (levetiracetam) became the first FDA-approved 3D-printed oral drug, marking a significant milestone and validating the regulatory potential of this novel manufacturing route [4]. In addition to drug delivery, the application of 3DP has extended into fields such as bio printing of tissues and organs, personalized nutrition, implant fabrication, and regenerative medicine, showcasing its versatility and far-reaching potential.[4]

Despite its advantages, the integration of 3D printing into routine pharmaceutical practice is not without challenges. Issues related to regulatory approval, quality control, scalability, material standardization, data integrity, and compliance with Good Manufacturing Practices (GMP) need to be addressed. Furthermore, the adoption of ALCOA+ principles (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, and Available) is crucial to ensure data integrity and traceability in digital and decentralized 3DP-based drug manufacturing environments. This review aims to explore the conventional 3D printing techniques applied in pharmaceutical sciences, discuss their benefits, limitations, and regulatory landscape, and examine their alignment with ALCOA+ principles for safe and effective personalized medicine.

1. Fundamentals of Data Integrity

In any database or additional storage system, integrity of data refers to the precision, regularity, and reliability of the data. It demonstrates that either data is being transferred, saved, or extracted. Data integrity management is an essential aspect of drug development, manufacturing, and regulation compliance as the pharmaceutical sector undergoes constant transformation. As the pharmaceutical industry continues to evolve, ensuring the accuracy, comprehensiveness, and dependability of data has become increasingly important in preserving the effectiveness, safety, and quality of pharmaceutical products. The term "data lifecycle" refers to all of the activities that include the production, documentation, interpreting applications, preservation, archiving, extraction, and deletion of information over the course of its whole lifespan. [5]

1.1. Types of Data integrity:

1. Physical integrity- Physical integrity is compromised once intruders disrupt the use of databases, natural calamities strike, or interruptions in electricity occur. System developers, software developers, auditing staff and data regulators cannot access precise info due to error by humans, storage subsidence, and other issues.
2. **Logical Integrity**: It secures from human error and hackers. Data integrity ought to be the primary concern while establishing a database that holds information. In response to this, an appropriate database is going to, once feasible and ensure data integrity. [6]

2.2. Importance of data integrity:

1. Safety and Effectiveness:

Data integrity ensures that drugs are used safely. It further demonstrates how they can operate when consuming medication. This is due to the reality that all production information is safeguarded. Data integrity must be appropriate in recognition of treatment to be beneficial.[6]

2. Accuracy:

Data integrity is essential in ensuring the appropriate use of drugs. It also demonstrates that reliance on treatment will make them effective. The reason is due to the protection of all manufacturing-related data.[6]

3. Effective production and distribution:

Following data integrity guidelines makes it easier to manufacture and distribute medications. Pharmaceutical firms utilize data integrity in developing the most effective medications feasible. It additionally assists physicians administer these drugs to the appropriate individuals.[6]

4. Trust Building:

Once pharmaceutical businesses' information is exposed, people find it hard to depend on them. Other organizations would also oppose to any sort of relationship. The confidentiality of information is essential to establishing and preserving confidence.[6]

3. ALCOA and ALCOA+ principles:

Regulated businesses use ALCOA (Attributable Legible Contemporaneous Original Accurate), a framework necessary for the application of Good Documentation Practices (GDPs), to guarantee data integrity. [7]ALCOA covers both paper and electronic data. Promoting data integrity efforts, maintaining GDPs, following GMPs, and maintaining an electronic and paper data handling system that satisfies standards all depend on the ALCOA principles.[8] In the 1990s, Stan W. Woollen of the FDA's Office of Enforcement was the first to adopt the abbreviation ALCOA. Complete, Consistent, Enduring, and Available (CCEA) was added to the ALCOA in 2010[8]. The terms ALCOA-C or ALCOA+ are more frequently used to refer to ALCOA-CCEA.[9]

Attributable:

Contributable The information generated or acquired must reveal the name of the individual who developed it, ensuring accountability. This gives you a record of who did what and when. [10]

Legible:

Reasonable Even in this digital age, readable data is not always readily apparent. It is true that maintaining legible and durable records is essential to maximizing data accessibility during the course of their existence. This also holds true for human-readable metadata that may be recorded to support an electronic record. It is crucial to remember that paper documents must be kept under control to prevent illegal duplication and that all records must be accessible and understandable by those with the proper authorization.

Contemporaneous:

Present-day Only at the moment of the observation or action must the data be documented. In addition to introducing mistakes or inaccuracies, delayed documentation may cause us to undermine the data's accuracy and quality.

Original:

The original It alludes to original data. Any alterations or modifications must be recognized and justified, and data must be recorded in its original format. This contributes to preserving the data's dependability.

Accurate:

The reality of what has transpired must be faithfully reflected in reliable data. It must accurately and truthfully represent the real data or observations. This principle highlights how crucial accuracy and precision are when capturing data.All pertinent topics should be covered with full data. Analysis and decision-making may be hampered by missing information.

Reliable: Data uniformity across many records and systems is ensured by consistency. Errors and misunderstanding can result from inconsistencies. Data should be long-lasting and maintain its integrity throughout time. Archiving, backup, and proper storage are always seen as crucial.

Available: Information has to be accessible for validation, examination, and review. Transparency and compliance depend on accessibility. Both digital and paper records must be readily available for inspections or investigations for the duration of the record. Both paper and electronic materials should have appropriate labeling and/or clear indexing to facilitate retrieval.[7,10] The overall ALCOA+ principles is illustrated in Figure 1.

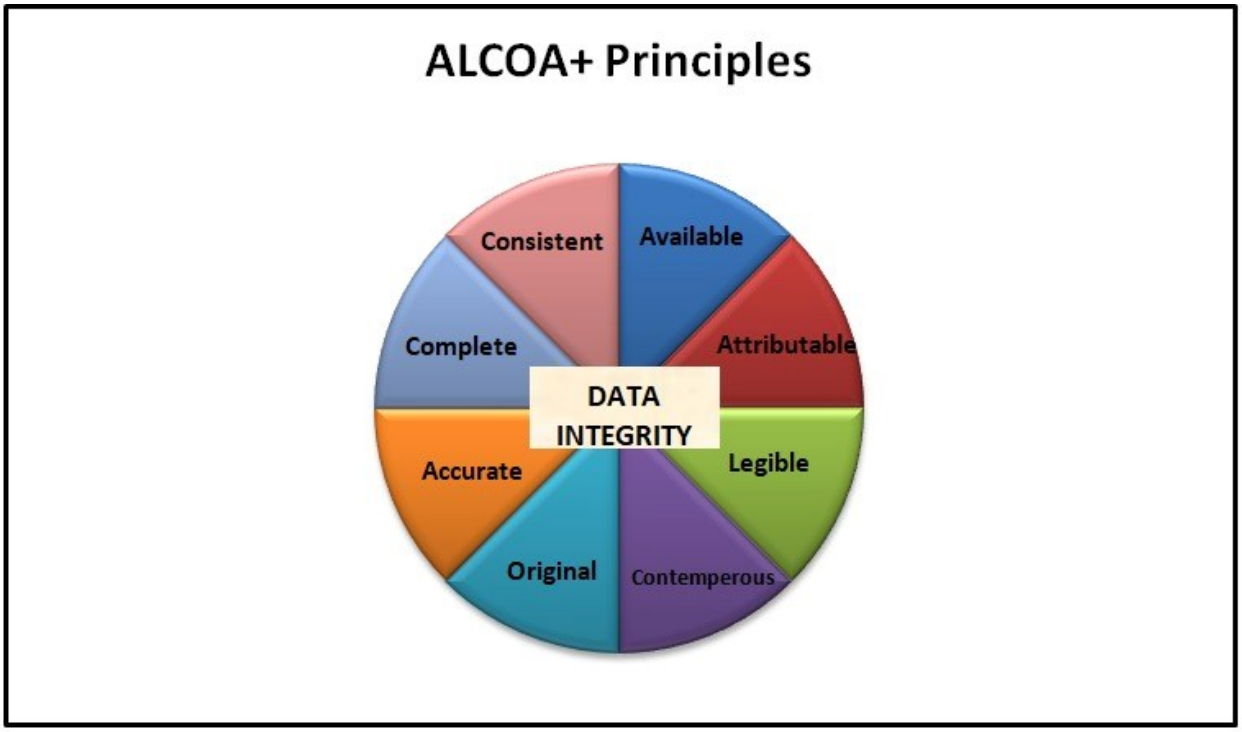

Figure 1: ALCOA+ principles are used for maintaining data integrity in drug manufacturing by highlighting the important characteristics: Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Available, and Enduring. ALCOA+ principles facilitate compliance with regulations and reliable electronic data management in technologies such as 3D printing.

4. CAD File Generation:

As a core pre-condition in the 3D printing process, the generation of a virtual 3D model plays a direct role in determining the final result of the printed object. Improved availability of personal 3D printers, especially within schools and among amateurs, has resulted in the increased need for CAD systems that are easy to use as well as accessible at a low or zero cost. Free and open-source CAD software support tools like FreeCAD and Onshape aim to address this need by combining easy-to-use tools for the production of solid models with no need for previous professional CAD skills.[11]

FreeCAD, for instance, is a parametric, feature-based CAD software that supports a modular architecture. It allows the user to create and modify geometric characteristics like sketches, constraints, and dimensions. While FreeCAD is not directly involved in 2D design or animation, it supports basic functionalities related to mechanical engineering and technical product development. CAD models developed through such applications are generally saved in the STL file format, which is widely supported in additive manufacturing. This exporting process involves settings such as units and resolution, which can be varied to accommodate the particular needs of the 3D printer. For models that incorporate colors or textures, though, the STL format proves insufficient because it carries only geometrical data in the form of triangulated tessellation. To circumvent this shortcoming, other formats such as VRML or STEP are advisable as they hold geometrical data as well as texture information.[12]

4.1. Design:

The design procedure with open-source or free CAD software generally takes the traditional route, beginning with 2D sketches that are extruded or revolutioned to form 3D solids. This procedure has its foundation in the constructive solid geometry (CSG) concept, which allows for the creation of standard mechanical features such as cuboids, cylinders, radii, chamfers, and holes. Other systems, like FreeCAD and Onshape, also include parametric modeling, allowing for the creation of dimensioned components that may be easily edited and reused on future projects.[13]

The paper classifies existing freeware CAD tools into three categories: mechanical construction tools, program-based tools, and creative design tools. Technical applications are best served by mechanical CAD systems, like FreeCAD, SketchUp, and Onshape, which offer tools for accurate modeling, assemblies, and dimensioning. Artistic design software such as Blender, however, are better suited to artistic use and organic modeling but are not geared towards mechanical design because their system is complicated to navigate and not programmatically driven.[13]

Evaluation of the CAD programs was performed based on usability, the presence of tutorials, quality of graphical user interface, and fundamental functions such as dimensioning, thread creation, and assembly support. Onshape ranked best in terms of feature completeness, with a full set of tools ideal for use in engineering, whereas FreeCAD was found to be the most comprehensive open-source software. Though possessing capabilities, freeware products usually are not permitted to access standard parts libraries, hence reducing their productivity in intricate design jobs handling commonly used hardware components.[14]

4.2. Product Workflow:

An uninterrupted product process from original design to ready 3D print—is necessary for effective prototyping and manufacturing. In the study under review, the authors show that freeware and open-source computer-aided design programs are becoming increasingly proficient in accommodating a full product development process. This involves the design of single components, the assembly of multiple parts, and preparation of models for additive manufacturing by compatible file exports. Onshape, specifically, was well suited to this process because it is a browser-based, cloud-native platform. It facilitates collaborative design through real-time file sharing, version control within the platform, and cross-platform accessibility, all of which are essential elements for distributed design teams.[15]

The tools' practicality was confirmed through a case study on designing and assembling a throttle valve. The parts were designed in Onshape, assembled digitally, and then printed using the STL interface from 3D printing with Binder Jetting technology. The procedure demonstrated not just the software's assembly and modeling prowess, but also how well it handled the phase transition to production in the physical world. Subsequent process steps like infiltration with epoxy resin were used to enhance the structural as well as aesthetic quality of the printed model.

Although existing tools are able, there are limitations particularly in the exchange of color and texture information and integration with simulation software. AMF and 3MF are being developed to improve data exchange, but these are still not commonly used. As freeware CAD solutions further advance, forthcoming developments will also feature closer integration with simulation packages, more robust support for collaborative workflows, and wider file format support, further solidifying their position in the end-to-end product design and manufacturing workflow.[15]

5. Introduction to Slicing in Additive Manufacturing[16]

In the world of Additive Manufacturing (AM)—more popularly referred to as 3D printing—slicing is a critical step that takes virtual 3D models and turns them into real, layer-by-layer physical products. While 3D modeling software such as SolidWorks, AutoCAD, or Fusion 360 produces intricate geometries, such models need to go through a translation process before a 3D printer can produce them. That translation process is slicing.

Slicing is the process of transforming a CAD file into thin horizontal cross-sections, which are then employed by a 3D printer to build the object from bottom to top. These layers are each defined in G-code instructions, which act as the printer's guide for head movement, extrusion speeds, temperatures, and rates.

5.1. slicing methodology

The 3D printing slicing process consists of a range of required steps, each responsible for the precision and quality of the final print. It begins with the translation of the 3D CAD model into an STL (Stereolithography) file, which describes the model's surface geometry in the form of a mesh of triangular facets. This is a highly compatible format between slicer software and has only the shape's critical information, so it is a speed-efficient format to work with. Once the STL file is imported into a slicer like Cura, PrusaSlicer, or Simplify3D, the model is sliced into thin horizontal layers—usually 0.1 mm to 0.3 mm thick—producing the series of steps the printer nozzle will follow along the Z-axis. Slicing proper is the term given to this step, which allows for accurate rendering of complicated shapes by approximating them with infinitesimal vertical increments. The slicer then creates the printer's G-code, which has precise movement commands (X, Y, Z), extrusion (E), and machine operations (M-codes) like temperature, fan, and pauses. The toolpath generated in the G-code also specifies perimeter passes, infill structures, top and bottom layers, and support material placement for overhangs. Advanced slicing software also includes adaptive layer heights, personalized supports, multi-material prints, and real-time G-code previews.

While slicing is paramount, the success of a print also depends on suitably chosen process parameters that influence its mechanical, thermal, and optical behavior. Vertical resolution and smoothness of surface print are controlled by layer thickness, with thin layers permitting higher detail but longer print time. Nozzle temperature governs material flow, adhesion, and surface finish, with optimal ranges depending on material (e.g., PLA: 190–220 °C, ABS: 230–250 °C, PETG: 220–250 °C). Bed temperature avoids warping and first-layer adhesion, especially for high-shrinkage materials like ABS that require 90–110 °C. Print speed must balance quality and throughput, with detailed prints printing at 30–40 mm/s and quick prototypes at 60–100 mm/s. Infill pattern and density manage internal strength of the part, employing geometries such as grid, honeycomb, or gyroid at densities from 5% to 100%. Travel and retraction settings avoid oozing and stringing while maintaining the nozzle in a definite position during non-print travel, and lastly, the synergy of accurate slicing and optimized parameters ensures high dimensional accuracy, smooth surface, efficient material utilization, and low risk of print failure. For example, successful printing of steep overhangs not only demands good-positioned supports in the slicer but also vigilant management of cooling, layer thickness, and reduced print speed in such regions.

5.2. Material extrusion:

Material extrusion, or Fused Filament Fabrication (FFF) or Fused Deposition Modeling (FDM), is among the most established additive manufacturing (AM) processes. It functions by extruding thermoplastic material in a layer-by-layer fashion to print three-dimensional objects from a digital CAD file. The process has broad application both in the industrial and consumer sectors owing to simplicity, material ease of accessibility, and relatively low operating expense.[18]

In a standard FFF configuration, a filament is propelled into a heatable nozzle by a gear or wheel that is controlled by a stepper motor. The filament is melted as it enters the liquefier and comes out through a small nozzle on to a build platform. The extruder head travels along toolpaths set by slicing software, building the geometry of the part in layers. Some of the critical parameters like layer thickness, print speed, nozzle temperature, and infill density have a direct impact on the mechanical and dimensional characteristics of the printed part.[18]

6. Drawbacks of Traditional Feedforward Control

In traditional material extrusion systems, the process is largely regulated by feedforward mechanisms. Slicing software calculates beforehand the extrusion rates required based on the target geometry as well as chosen print parameters. These commands are run without the use of real-time feedback, which creates a number of difficulties:[19]

Sensitivity to outside disturbances: Changes in bed leveling, room temperature, filament thickness, or material variations can impair print quality.

Under- or over-extrusion: Material flow inaccuracies can lead to dimensional errors, surface finish defects, and poor inter-layer adhesion.

Limited flexibility: Inelastic extrusion parameters are not responsive to curing transient errors or anomalies during printing.

Dependency on empirical tuning: Achieving optimal results often requires extensive trial-and-error, which is time-consuming and non-transferable between printers or materials. These shortcomings highlight the need for more intelligent, adaptive control mechanisms in material extrusion.

Force Controlled Printing: A Closed-Loop Approach

In order to overcome the shortcomings of open-loop control, new research has suggested a new methodology called Force Controlled Printing (FCP). This closed-loop control approach brings in an extrusion force sensing feedback-based real-time mechanism, which fundamentally changes the control paradigm in FFF.[19]

Principle and Architecture

FCP is based on the fact that there is a high and reliable correlation between the extrusion force and the extruded line width. By constantly measuring the force needed to extrude filament out of the nozzle and onto the building surface, the system adaptively controls the extrusion feed rate to keep the target force at a constant value. This is done with a specially designed extrusion head that has a torque sensor, which returns high-resolution measurements on the filament drive force.

The extrusion controller uses a tuned PID algorithm with both high-frequency and damped derivative terms to address disturbances from machine dynamics and variability in filament flow. The closed-loop system provides real-time compensation for disturbances like drive slippage, uneven surface contact, and temperature fluctuation.[18,19]

Material Considerations [19]

FCP approach was experimentally verified on Liquid Crystal Polymers (LCPs), which are a group of high-performance thermoplastics characterized by directional mechanical strength and thermal stability. LCPs are specifically sensitive to extrusion conditions and, hence, a good benchmark to test control fidelity. Precise force control was crucial to maintain molecular alignment and ensure maximum mechanical performance in printed components.

Experimental Validation

A series of experiments were performed to compare the performance of FCP with conventional feedforward extrusion:

Line Width Control: A linear correspondence (R^2 = 0.99) was found between reaction force applied and resulting line width, allowing accurate control over geometric output. Line widths from 33% to 233% of nozzle diameter were printed successfully using a single nozzle.[20]

Bed Leveling Compensation: FCP exhibited stable line width even when subjected to artificially tilted print bed situations. The method showed a 54% decrease in RMSE of line width as compared to regular printing.

Fault Tolerance: In simulated filament slippage conditions, FCP compensated dynamically for under-extrusion by boosting drive speed, whereas the traditional method produced major defects and material starvation.[20]

7. **Data Integrity Risks in 3D Printing**:

Additive Manufacturing (AM), also known as 3D printing informally, is gradually changing the way industrial processes are approached due to its flexibility, the ability to shorten prototyping time, and the elimination of surplus. At the same time, digitization and interconnection of modern manufacturing contribute to the emergence of new risks in terms of data integrity. Such weaknesses may affect the quality, safety, and security of the produced artefacts, especially in critical industries like aerospace, medical devices, and defence. [21]

7.1. Design File Tampering (CAD/STL/G-code Corruption):

Fellow employees, 3D printing uses three types of digital files, namely, CAD, STL, and G-code, to encode the geometric information and printing instructions. These files and derivatives thereof have to be considered subject to careful inspection, as they are subject to intentional or unintentional alteration. Belikovetsky et al. (2016) have carried out a formative study: even a small variation in the G-code of a drone propeller led to an occurrence of mechanical failure during the operation. In the findings, the limited structural integrity and component performance can be weakened at any level of digital interventions.

Such alteration can be unnoticed in mass production, especially when run with automated slicing requirements and unmonitored printing schedules. This latitude can be abused by malicious actors who can be instilled with hidden defects in an undetectable manner or by modifying interior geometries. Critical parts of aerospace or medical products are particularly unwelcome victims of tampering.[22,23]

7.2. Firmware and Controller Software Manipulation

Firmware is more of the functional layer that defines the way 3D printers interpret and process the sets of instructions. Malicious firmware profiles can change printing properties secretly, thus influencing the part strength, infill, and temperature profiles. Pearce et al. (2022) showed that the attacking program is placed in printer firmware as malware named FLAW3D, so it erodes structural integrity with no outside signs.

Attacks executed on the firmware have a large risk potential since they run on the foundational level of the application and are hard to detect. When infiltrated, firmware can spread among networked printers, or can be caused to go off remotely to create synchronized attacks to cripple multiple production lines. Constant firmware updates and stringent validation procedures are thus essential to the alleviation of such dangers. [24]

7.3. Data Interception During Transmission

Lately, inter-software, the cloud and communication between the printers in additive manufacturing (AM) systems are getting exposed to interception via the insecure networks. According to Do et al. (2016), the transmission channels can be exploited by a remote intruder to either intercept or alter the print files in transmittal, a situation that impairs data authenticity and integrity. These weaknesses are normally caused by the lack of a sufficient encryption protocols or weak authentication schemes. Although cloud slicing services and remote monitoring platforms raise the overall efficiency of operations, they also make sensitive data vulnerable to the man-in-the-middle attacks. Therefore, encryption, virtual private networks (VPNs) and secure application programming interfaces (APIs) ought to become a default design conduct in the modern AM systems. [25]

7.4. Insider Threats and Unauthorized Access

A 3D printing facility can be used to implement structural alterations in the form of actors without notice, or to leak intellectual work to them. Beckwith et al. (2021) explore the challenges of malicious G-code script detection so that it can be used to impair the overall performance of the output printed parts.

In environments at a high level of security, strict control over access is one of the decisive barriers. Role based authorisation, timely real time logs and real-time monitoring are positives of detection and prevention of unauthorised activities and malicious activities. In parallel, a thorough training of employees and constant awareness campaigns is also essential to help address weaknesses introduced by human concepts of cognition and work [26]

7.5. Supply Chain Tampering: Hardware and Software Trojans

Printers may have long-lasting vulnerabilities resulting from alterations the construction of hardware or embedded software, or later maintenance, introduced with malicious intent. Here, Basu et al. (2023) proposed a hardware/software Trojan taxonomy that can appear in the course of digital manufacturing.

These risks tend to be initiated by outward suppliers and vendors, hence the significance of intensive vetting systems and implementation of safe entity design techniques. Components-level checks, intensive supply chain audits, and hardware root-of-trust technologies can be deployed to foster safer manufacturing ecosystems. [27,28]

7.6. Insecure Cloud-Based Platforms

The use of cloud service in file slicing and storage introduces some new security issues. Wang et al. (2022) offer a blockchain solution to ensure file integrity both in storage and in the transfer of this information. With the cloud services communicating with huge user communities and with third party design or post processing tools, the entire attack surface spikes. Blockchain allows documenting file access events and any changes in an immutable untamperable ledger hence providing transparent audit trails and identifying any changes. [29]

7.7. Version Control and Traceability Issues

Unless version management is comprehensive, it is possible to accidentally print older or modified files, which also happens due to personal negligence and systematic abuse. Digital signatures and blockchain technology are also being considered as the possible identifiers of safe version control.

In addition, well-established traceability frameworks are capable of supporting product recalls and warranty claims hence enhancing responsibility throughout the production cycle. This is very essential, particularly on regulated area segments, where each printed part must meet demanding requirements on traceability. [29]

8. Good Documentation Practices (GDP)

Paper vs. Electronic Documentation

Documentation in 3D printing ensures traceability, regulatory compliance, and process reproducibility. Traditional paper-based records offer simplicity and regulatory acceptance but are susceptible to errors, loss, and inefficient retrieval. They are best suited for smaller operations with limited digital infrastructure. Conversely, electronic documentation enhances efficiency through searchability, real-time updates, and integration with digital workflows. It supports compliance with standards like 21 CFR Part 11 but requires robust cybersecurity and training. Hybrid systems combining both approaches are often used during digital transitions to balance reliability and modernization. [30]

- Discusses documentation needs in additive manufacturing, emphasizing electronic systems for scalability. [31]

Requirements for Printing Logbooks and Design Records

Printing logbooks must record essential parameters such as material specifications, printer settings (e.g., nozzle temperature, print speed), and environmental conditions to ensure process repeatability. These records require clear timestamps, operator details, and tamper-proof mechanisms to meet regulatory standards. Design records, including CAD and STL files, should document design inputs, outputs, and version histories, ensuring traceability and audit readiness. Secure storage and access controls are critical to protect intellectual property and comply with retention requirements, such as those mandated for medical devices (typically 7 years). [32]

- Specifies documentation standards for quality assurance in manufacturing.

- Highlights the need for detailed logbooks in 3D printing for medical applications. [33]

Electronic Batch Records (EBR)

Integration with Printers and Software

EBRs automate the collection of 3D printing data, improving efficiency and reducing manual errors. They integrate with printers through APIs, capturing real-time data like layer counts or error logs, and connect with Manufacturing Execution Systems (MES) for centralized data management. IoT-enabled sensors enhance monitoring by recording environmental factors. Compatibility across diverse printer brands and software updates poses challenges, necessitating standardized data formats (e.g., JSON) and staff training to ensure seamless operation. [34]

Ensuring Data Authenticity and Backup

To ensure data integrity, EBRs employ electronic signatures and audit trails to track modifications, aligning with regulatory standards like 21 CFR Part 11. Advanced methods, such as cryptographic hashing, enhance tamper resistance. Regular backups (e.g., daily incremental, weekly full) to secure cloud or on-premises servers prevent data loss, with encryption safeguarding sensitive information. Periodic validation of backups and adherence to retention policies (e.g., 5–10 years for regulated industries) are essential for compliance and recoverability. [35]

Design File Validation and Approval

File Versioning, Change Control, Design Qualification

Effective version control ensures design file integrity by assigning unique identifiers to iterations and tracking changes via systems like Git or PLM software. A structured change control process evaluates modifications, requiring detailed justifications and stakeholder approvals to maintain compliance. [36] Design qualification verifies that files meet functional and regulatory requirements through simulations (e.g., stress analysis) and compatibility checks with printer capabilities, ensuring printability and performance. [37]

- Covers design validation and version control in 3D printing.
- Defines standards for design processes in additive manufacturing.

QA's Role in Approving and Archiving Print Parameters

Quality Assurance (QA) ensures print parameters align with design specifications and regulatory requirements by reviewing settings like layer thickness and material certifications. [38] Automated workflows in EBR systems streamline approvals, while QA oversees secure archiving of parameters with metadata for traceability. Archives must comply with retention periods (e.g., 7 years for medical devices) and use encryption to protect data. Regular audits by QA ensure documentation integrity and regulatory compliance. [39]

Synthesis and Implications

This review highlights the critical role of robust documentation in 3D printing, particularly for regulated industries like aerospace and medical device manufacturing. Electronic systems (EBRs, version control) offer significant advantages in efficiency and compliance but require investment in cybersecurity and training. Paper-based systems remain viable for smaller operations but are less scalable. QA's oversight in validation and archiving ensures traceability and regulatory adherence. Future research should focus on standardizing EBR integration across diverse 3D printing platforms and enhancing cybersecurity for design files. [39]

Regulatory framework in 3D printing:

The residual uncertainty in the regulatory domain revolves around whether the typical 3D printer should be treated as a medical device or only the end product thereof should be subject to regulation. This line of distinction is very important, as it affects the way the documentation and compliance processes are structured in the manufacturing and healthcare frameworks. [40]

Operator Skill Importance and Printer Accuracy

Printing outcome can vary for moderate- to high-risk medical devices for reasons such as printer precision, technician skill, or controlling software. Hence, each step from digital modeling right through to the final print must be documented and validated to avoid error. To provide for regulatory oversight and traceability, it is required that printers be held to a defined standard of accuracy. [40]

Need to Regulate the Entire Chain

A product can fail due to design flaws, or imperfections in materials, or fabrication causes. It is therefore clear that regulations must apply to input materials and the entire manufacturing process. This calls for a comprehensive documentation approach which will encompass files of design, material certifications, calibration logs of printers, and records of environmental control. [40]

Quality Control during Integrated Production

Unlike in traditional manufacturing systems where the possibility of quality checking after production was feasible, 3D-printed medical products are often used shortly after fabrication. Hence quality assurance must be embedded within the production workflow. This means that one needs to acquire data in real time, ensure that the data are logged digitally, and implement validation protocols in the process. All should be compliant with data integrity standards, which would minimize the requirement to do extensive testing after the 3D printing process.

9. 21 CFR part 11 in data integrity and 3D printing:

Robust data integrity checks embedded within the MES provide great leverage toward fulfilling compliance requirements under the umbrella of global regulatory frameworks such as 21 CFR Part 11, 21 CFR Parts 210 and 211, ICH Q7, and EudraLex Volume 4 Annex 11. These controls ensure GMP-relevant data generated and used throughout the product lifecycle are accurate, consistent, and traceable.

Analytical and scenario-based evaluations support the realization of functionalism within MESs, whereby processes such as automated data acquisition, secure and immutable audit trails, and transfers of validated data boost not only regulatory compliance but also operational efficiency, prosperity with regulatory inspections, and inspection readiness. [40]

Automated Data Acquisition: Device integration through the OPC UA protocols permitted unattended recording of critical parameters; for instance, weight-noted reduction in manual entry errors by 30%, serving compliance under 21 CFR 211.101. Audit Trail Compliance: Secure audit logs, recording users and time stamps for events, were implemented to complete traceability, in alignment with expectations under 21 CFR Part 11 [41].

10. QBD AND RISK ASSESSMENT IN 3D PRINTING AND DATA INTEGRITY:

The embedding of QbD principles in pharmaceutical 3D printing leads to a structured approach to ensuring product quality, regulatory conformity, and data integrity. During the design phase of a semi-solid extrusion (SSE) 3D printer for personalized medicines, with respect to table 1 the risk assessment tools were capitalized upon to evaluate critical process parameters (CPPs), namely cartridge preheating temperature, extrusion speed, and nozzle calibration; these parameters were identified as those with potential high impact on critical quality attributes (CQAs) such as drug content uniformity, release kinetics, and mechanical strength. Incorporating-enforced data integrity using software that observed GAMP5 standards with secure user login, the software monitored recording production parameters in real-time. This audit trail traces and supports analyzing root causes, which are all prescribed under 21 CFR Part 11. Additionally, feedback control systems with precision thermistors ensured that the thermal profile was kept consistent and minimized the chance of deviation. These control and documentation approaches thus enhance manufacturing reliability on the whole while also meeting the expectations of the FDA and EudraLex Annex 11 [42].

Table 1: **RISK ASSESSMENT TOOLS USED IN 3D PRINTING WORKFLOW:**

S.NO	TOOLS	USES IN 3D Printing
1	FMEA	Identification of critical failures
2	FISH BONE DIAGRAM	Root cause of variability and defects
3	RAE MATRIX	Assigns risk by score: severity, occurrence, detectability

4	HACCP	Focuses on contamination and procedural control points
5	DoE	Definition of the control space for critical parameters
6	PAT	Real-time quality monitoring
7	GAMP5 + Audit Trails	Ensures compliance with 21 CFR Part 11 and EudraLex Annex 11

11. BLOCKCHAIN TECHNOLOGY IN DATA INTEGRITY:

Blockchain technology introduces a decentralized and secured infrastructure, thereby enhancing the traceability and integrity of data within the additive manufacturing (AM) lifecycle. In this chosen quality assurance system, each step-from the generation of CAD files to the partial finishing of the final product-is recorded on the blockchain in chronological and immutable form. The blockchain records related metadata, including file or drawing versions, build parameters, machine configurations, environmental parameters, etc., thus safeguarding the integrity and truthful nature of production or manufacturing records. Automated validation may be achieved by executing smart contracts on the blockchain at critical stages, hence ensuring a very small manual interference and hence lessening the chance of human error. Using this system further protects digital assets and prevents unauthorized alteration of design files and G-codes while allowing full traceability. With blockchain applications in AM workflow, reasonable assurance is given that the data integrity requirements set forth by 21 CFR Part 11 are maintained, including secure user access, audit-trails, and long-term trustworthy data storage [43].

12. Challenges in 3d printing technology:

Pharmaceutical 3D printing raises originality concerns under ALCOA+ due to potential manipulation of digital manufacturing files and sensor generated data. A 2023 study in Journal of Pharmaceutical Innovation proposed using private blockchain networks with proof of authority and smart contracts to ensure tamper proof data logging. By cryptographically hashing and time stamping production reports, their system detected falsified records with high accuracy even after injecting known data-tampering events thereby enforcing the "Original" ALCOA+ principle in a scalable way.[44] . While promising, adapting such blockchain embedded architectures to decentralized or point of care 3D printing environments remains an open challenge.[44]

Simultaneously, broader accuracy and consistency issues emerge from variability in printer calibration, formulation rheology, environmental controls, and limited quality control standardization across platforms[45]. As described in recent Biomedical & Pharmacology Journal and Pharmaceutical Research reviews, void formation between printed layers, material anisotropy, formulation stability, and printer tolerance all threaten dose uniformity and reproducibility across batches or sites.[46]

Furthermore, regulatory frameworks like those from FDA, MHRA, WHO, and GAMP-5 emphasize the need for validated computerized systems, real-time process monitoring (e.g. via PAT), and integrated electronic data management to uphold all ALCOA+ tenets—but widespread implementation in additive manufacturing remains nascent.[47]

CONCLUSION

The intersection of three-dimensional printing (3DP) and data integrity procedures represents a revolutionary period in pharmaceutical production, where innovation is met with stringent quality control. As this review has demonstrated, 3DP presents unparalleled means of adapting drug delivery systems to the unique requirements of individual patients, facilitating precise management of dosage form geometry, drug release kinetics, and polypharmacy incorporation. The FDA approval of Spritam® has already established the potential of 3D-printed pharmaceuticals, and the wave of personalized medicine, especially in pediatrics, geriatrics, and rare disease patient populations, keeps moving ahead.

However, the success of 3DP in mainstream drug practice depends not only on technical performance, but on the strength of data governance systems that guarantee safety, effectiveness, and conformity. Data integrity, informed by ALCOA+ standards, permeates the entire 3D printing life cycle—from CAD file creation and slicing through printer calibration, documentation, and quality control. With 3DP more decentralized and dependent on digital ecosystems, threats like design file manipulation, firmware tampering, and insecure data exchange need to be actively counteracted by technologies such as blockchain, real-time audit trails, and encrypted communication protocols,.

Additionally, the combination of Good Documentation Practices (GDP) and Electronic Batch Records (EBRs) facilitates traceability, standardization, and regulation, particularly where medical devices or pharmaceuticals are printed near the point of use. Regulatory schemes like 21 CFR Part 11, ICH Q7, and EudraLex Annex 11 highlight the importance of automated data acquisition, tamper-proof records, and real-time validation—features that can no longer be secondary, but need to be integrated into the additive manufacturing process.

A common thread running through this review is the imperative of system-wide validation and process control, especially by Quality by Design (QbD) and risk assessment tools such as FMEA, HACCP, and PAT. These frameworks, in addition to adaptive feedback mechanisms such as Force-Controlled Printing, are critical tactics for managing the intrinsic variability of feedforward-based extrusion and guaranteeing reproducibility, accuracy, and mechanical integrity from batch to batch and from platform to platform.

But there are still challenges. Printer performance variability, the absence of global standards, regulatory uncertainty regarding device-versus-product classification, and issues of establishing authenticity across cloud-based or decentralized systems continue to pose significant obstacles to wide-scale adoption. Studies in secure architectures—e.g., private blockchains, smart contracts, and AI-augmented validation tools—have to be pushed forward in parallel with developments in hardware and material science.

In short, even as 3DP promises to transform pharma production by customizing, streamlining, and enabling point-of-care availability of drugs, its sustainable integration can be achieved only through an integrated approach—one that strikes a balance between technological advancement and robust data integrity, regulatory control, and process management. The pharmacy of the future will not be established by how drugs are printed, but by how securely, transparently, and reliably they are produced from digital to physical streams of data.

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