Review Paper

Quality Assurance in Decentralized Manufacturing: A Review of Validation Frameworks for 3D-Printed Personalized Medicines

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Abstract

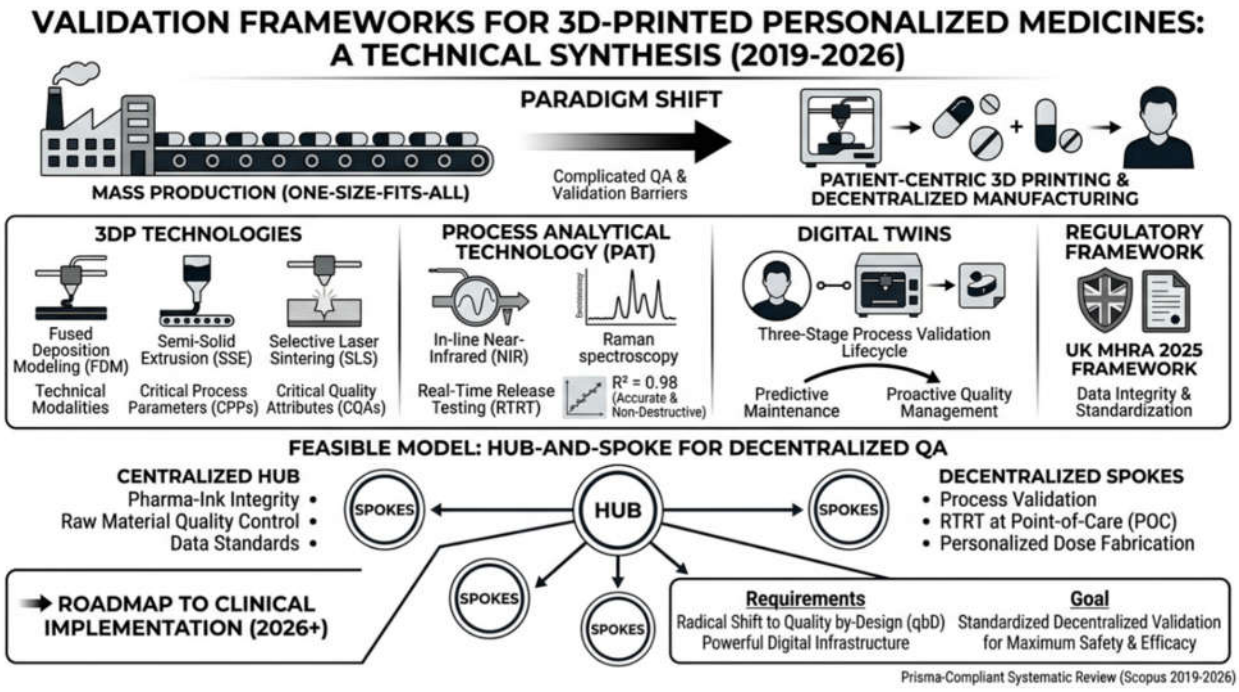
Background The pharmaceutical industry is in a paradigm shift in which the mass-production model based on one-size-fits-all is being replaced by the patient-centric model that is made possible by three-dimensional printing (3DP) and decentralized manufacturing (DM). Although 3DP enables the personalization of dosage form as never before, the translation of the technology into clinical practice is complicated by the complicated quality assurance (QA) and validation barriers. Purpose: This review critically synthesizes the existing validation frameworks of 3DP personalized medicines with special emphasis on the combination of Process Analytical Technology (PAT), Digital Twins, and the recently implemented UK MHRA 2025 regulatory framework. Methodology: Scopus-indexed literature (20192026) was searched in a PRISMA-compliant systematic search that focused on point-of-care (POC) manufacturing, real-time release testing (RTRT), and data integrity. Core Mechanisms: We consider technical modalities, such as Fused Deposition Modeling (FDM), Semi-Solid Extrusion (SSE), and Selective Laser Sintering (SLS), their respective Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs). Findings: The review identifies the Hub-and-Spoke model as the most feasible structure of decentralized QA with centralized hubs that address the issue of integrity of the pharma-ink and decentralized spokes that address the issue of process validation. In-line Near-Infrared (NIR) and Raman spectroscopy technologies that enable the real time release of doses are accurate and non-destructive (R 2 = 0.98) and allow real time verification of doses. Moreover, the Digital Twin technology improves three-stage process validation lifecycle, providing predictive maintenance and proactive quality management. Conclusion: To attain sustainable clinical implementation of the 3DP, a radical change toward Quality-by-Design (QbD) and a powerful digital infrastructure is required. In the coming 2026 and beyond, we suggest a

roadmap to standardize decentralized validation to achieve the best safety and efficacy of personalized medicines.

Keywords

Additive manufacturing; point-of-care manufacturing; quality-by-design (QbD); Process analytical technology (PAT); Digital twin; ALCOA +; decentralized manufacturing; regulatory framework; personalized medicine; Pharma 4.0.

Graphical Abstract



1.Introduction

The present pharmaceutical environment is shifting radically towards the standardized mass-production approach of the one-size-fits-all solution to a patient-centric model facilitated by 3DP and decentralized manufacturing (DM)[1]. Traditional production has traditionally been streamlined towards high-speed tablet and encapsulation, yielding identical units that may not typically consider the inter-individual differences in genetics, age, and disease condition. This inflexibility results in sub-optimal treatment results or adverse drug reactions (ADRs) among large patient subgroups. The driving force of this change is mainly the use of 3D printing (additive manufacturing) (AM) to enable the creation of custom dosage forms, layer-by-layer, within digital designs at the point-of-care (POC). This right drug, right patient mandate cannot be implemented successfully without overcoming complicated issues in the quality assurance (QA) and process validation in the context of decentralized settings[2].

Such a transformation should be thoroughly reviewed based on a PRISMA-conforming systematic search of Scopus-indexed publications published between 2019 and 2026. This approach guarantees resistance and scholarly influence by classifying interconnected obstacles into a structural, intermediate, and fundamental level. The review assesses the small molecule and biologic manufacturing processes, including the Industry 4.0 concepts of cyber-physical systems and big data analytics to overcome the gap between regulatory flexibility and technical innovation[3]. This systematic method is necessary in proving the digital thread between a clinical prescription and the end printed medicine.

The essence of decentralized validation structures is based on a profound insight into technical modalities and their key process parameters (CPPs). Extrusion technologies, including Fused Deposition Modeling (FDM) and Semi-Solid Extrusion (SSE), are popular because of their low cost and ability to convert solid-state material. FDM aids in producing amorphous forms of APIs by thermally extruding crystalline forms, which improves bioavailability of BCS Class II and IV drugs but is restricted by high processing temperatures[4]. SSE seeks to overcome these thermal constraints by treating pastes at room temperature, but at the cost of introducing time-consuming curing stages. Selective Laser Sintering (SLS) uses powder-bed fusion methods that can produce porous structures that disintegrate quickly but that are vulnerable to thermal degradation, whereas vat photopolymerization (SLA) has better resolution but is limited to biocompatible resins.

A basic change in the system of quality assurance in decentralized environments is the abandonment of the old methods of destroying end products to the real-time, non-destructive Process Analytical Technology (PAT). The traditional chromatographic technique (e.g., HPLC) is time-consuming and not possible to scale to small-batches POC production. Decentralized QA uses miniaturized near-infrared (NIR) and Raman spectroscopy as the sensory apparatus to facilitate real-time release testing (RTRT). The in-line NIR systems have been proven to measure the drug load in efavirenz printlets with high linearity (), and accuracy[5]. Raman spectroscopy, in a similar manner, is able to offer highly accurate monitoring of solid-state conversion so that the personalized dosage is in the appropriate amorphous or crystalline form without damaging the sample.

The most popular architecture of the decentralized supply chain is the so-called Hub-and-Spoke design, where final fabrication is addressed by decentralized spokes, and the integrity of pharma-ink is controlled by centralized hubs. In 2025, the UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a legal framework that is the world-first with regards to the manufacturing of POC. This legislation brings in the concept of the "Point of Care Master File" which enables several manufacturing sites to be run under one control hub which is the control site yet with high standards of Good Manufacturing Practice (GMP)[6]. This model enables life-saving therapies, which have short shelf life, to be made at the bedside of the patient, cutting months to days in wait times and enabling the virtual ward models.

The most important and the most significant part of the modern validation frameworks is the inclusion of Digital Twins in the process validation lifecycle. A Digital Twin is a dynamic virtual replica of the actual manufacturing process, which improves Stage 1 (Process Design) by virtually experimenting, Stage 2 (Process Qualification) by predicting full-scale behavior, and Stage 3 (Continued Process Verification) by proactively detecting faults. The model-driven approach is consistent with Quality-by-Design (QbD) concepts, where the Design Space is used to guarantee that quality is a natural product of scientific knowledge and not a terminal point. The Digital Twin has artificial intelligence and machine learning as the brain that processes sensor data to optimize manufacturing in real-time[7].

Validation should also accommodate biological and clinical difference, especially the effect of pharmacogenomics and sex difference on the response of drugs. Drugs such as efavirenz or warfarin, where genetic differences in enzymes of metabolism (e.g., CYP2B6 or CYP2C9) may cause toxicity or lack of effect, are influenced by individual dosing. Age-specific mini-printlets in pediatric patients and multicomponent polypills in geriatric patients can be age-appropriate with 3DP, enhancing adherence and simplifying treatment regimens. Such personalized results are fundamental to precision medicine, guaranteeing that a form of dosage suits an individual physiological and genetic phenotype[8].

Lastly, decentralized 3DP poses considerable cybersecurity challenges that should be addressed to guarantee data integrity[9]. Regulatory compliance requires adherence to ALCOA+ principles (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available). A solid solution is presented by blockchain technology as it offers an unalterable online registry to ensure the digital thread, between prescription and print, is not tampered with, sabotaged, or changed remotely. Although variability in printer performance, and global standards remain concerns, the convergence of QbD, PAT, Digital Twins, and blockchain offers a strategic way forward to safe and sustainable delivery of personalized 3D-printed medicines in 2026 and beyond[10].

2. Literature selection methodology:

The methodology of literature selection of this systematic review is built on a strict systematic methodology that will provide academic transparency and high-impact validity and compliance with PRISMA (Preferred Reporting Items to Systematic Reviews and Meta-

Analyses) criteria. The main goal of this methodological framework is to integrate and critically analyze the complex issues related to the application of three-dimensional printing (3DP) and decentralized manufacturing (DM) in the clinical and pharmaceutical context[11]. To do this, a multi-stage search plan was implemented in three main high-impact databases: Scopus, PubMed, and Web of Science, which included the years 2019-2026. This particular time frame was chosen in order to include the speed of technological acceleration and regulatory change that followed the 2015 FDA approval of the first 3D-printed tablet and the resultant worldwide shift towards resilient, point-of-care (POC) healthcare delivery patterns. Peer-reviewed literature and authenticated regulatory materials indexed in Scopus were used as the only source of search to ensure the highest level of evidence-based research[12].

The search architecture involved a set of Boolean operators and sets of keywords that were meant to cut across the technical, digital, and regulatory aspects of the field. The terms were: Additive Manufacturing, Pharmaceutical 3D Printing, Decentralized Manufacturing, Point-of-Care Manufacturing, Quality Assurance, Process Validation, Digital Twin, Process Analytical Technology (PAT), and ALCOA+. In order to cover the digital thread comprehensively, several more strings associated with Industry 4.0 principles, including, but not limited to, "cyber-physical systems," blockchain to guarantee data integrity, and big data analytics were added to the search protocols. Through this method, it was possible to identify literature covering the structural engineering of dosage forms as well as the digital infrastructure needed to authenticate them in non-traditional manufacturing environments[13].

Screening and selection was conducted under a standardized dual-reviewer protocol to reduce selection bias and assure that only the best, most relevant studies were included in the final synthesis. The first round of screening was conducted based on the title and abstract, and the studies that presented empirical evidence on validation framework or offered new approaches to quality assurance (QA) of 3D-printed medications were selected. The shortlisted articles were then subjected to full-text analysis with certain inclusion criteria being used to identify studies that covered both biologic manufacturing processes and small molecule pharmaceuticals[14]. The dual-scope procedure guarantees that the overview depicts the pharmaceutical range, simple to fabricate pills and complicated advanced therapy medicinal products (ATMPs). The research studies that had narrowed down to just prototyping without regarding regulatory compliance or GMP standards were not included in the research as the essence of the entire research is to offer a translational road map to clinical integration.

An inductive analysis of the data was carried out by means of thematic analysis, the organization of which was performed with the help of the professional qualitative research program NVivo 15. It was done with a two-level descriptive coding scheme in which unique pieces of data were manually labeled and grouped into descriptive themes. The development of these descriptive themes was then repeatedly evolved into an analytical theme on a higher level that signifies the current state of research and the existing gaps in knowledge[15]. This approach helped to design a hierarchical thematic framework that is classified into three levels of interconnected barriers to 3DP adoption structural, intermediate, and fundamental factors. Through this hierarchical framework, the review is able to state the inadequacy of

advances in technical innovation without the consequential changes in digital preparedness and regulatory policy.

The middle tier in the thematic framework deals with the operational/digital maturity gaps that stop 3D-printed medicines scalability. Among the essential themes that were discovered during this tier, there is the incorporation of the Digital Twin technology and artificial intelligence (AI) as the means of ensuring the process comprehension and anticipating critical quality attributes (CQAs). The literature review focuses on how digital twins can be incorporated into the three-stage process validation lifecycle (Process Design, Process Qualification, and Continued Process Verification) to facilitate proactive, real-time quality management. Moreover, the role of non-destructive PAT tools, especially miniaturized Near-Infrared (NIR) and Raman spectroscopy, in supporting real-time release testing (RTRT) at the bedside is assessed at this tier[16].

The basic tier of the thematic framework underlines that sustainable integration of 3DP is facilitated by systemic preparedness by means of adaptive control and sound digital quality infrastructure. The level deals with the digital-to-physical workflow and cybersecurity-specific risks of internet-connected manufacturing devices. Themes of data integrity, supported by the ALCOA+ principles, and possible opportunities of blockchain technology to safeguard the so-called digital thread and guarantee intellectual property are discussed in detail. Synthesizing these three levels, the methodology offers a holistic view of interdependencies among technical innovation, ethical legitimacy, and regulatory flexibility.

3. Core Mechanisms and Technical Modalities:

To develop a decentralized pharmaceutical production system with a comprehensive validation framework, a deep knowledge of the technical modalities that are fundamentally driving three-dimensional printing (3DP) is required. A radical shift in thinking about quality-by-inspection to Quality-by-Design (QbD) is necessary to transform the traditional centralized mass production with a high speed of unit operations such as tableting and encapsulation to point-of-care (POC) 3DP production[17]. All 3DP technologies have a distinct mechanical architecture and material processing principle, which, in turn, determines its own Critical Process Parameters (CPPs) and consequent Critical Quality Attributes (CQAs) of the final dosage form. In this sense, validation does not just relate to the verification of the end product but to whether or not the process of layer-by-layer fabrication is controlled and continuous even though decentralized environments are variable.

Fused Deposition Modeling (FDM) is the most researched extrusion-based technology in the pharmaceutical field, mainly because it is cost efficient, accessible and mechanically straightforward. The basic principle is that a drug-functionalized thermoplastic polymeric filament is fed through a heated nozzle whereby the material is melted and deposited on a build platform in a pattern of choice. In the context of validation, FDM presents a great technical benefit: the thermal extrusion process can be used to convert an active pharmaceutical ingredient (API) into an amorphous form as opposed to its crystalline form[18]. This creation of amorphous solid dispersions is essential in increasing the solubility

and bioavailability of drugs with BCS Class II and IV. Nevertheless, high processing temperatures, which are usually between and -impose a major material limitation, as they can lead to the thermal degradation of thermolabile APIs or thermodegradable polymers. FDM validation schemes must thus consider nozzle temperature and residence time as high-impact CPPs to provide API stability but remain at required melt viscosity to provide structural integrity.

The relatively more recent Semi-Solid Extrusion (SSE) or Pressure-Assisted Micro-Syringe (PAM) printing is a more flexible substitute that addresses thermal constraints of FDM. SSE is used to extrude drug-loaded pastes or gels at or near room temperature, instead of melting solid filaments, with the aid of pneumatic or mechanical pressure. This gentle processing condition renders SSE especially appealing to heat labile compounds, such as peptides and biological drugs. Although this is a plus, the application of SSE in decentralized environments presents new validation problems pertaining to solvent management. Recipes frequently involve the use of the hydro-alcoholic solutions in order to obtain the rheology required to extrude smoothly, which in turn requires a lengthy curing or drying period. This is a post-processing step that may result in shrinkage or deformation of the printed pill, which may affect the dimensional accuracy and uniform dosage. As a result, extrusion pressure, material viscosity, and drying conditions should be the primary aspects of validation of SSE processes that determine the future mechanical strength and release profile of the final printlet.

Table 1: 3D Printing Modalities and Their Pharmaceutical Applications

Modality	**Core Mechanism**	**Key Advantages**	**Major Limitations & Risks**
Fused Deposition Modeling (FDM)	A drug-functionalized thermoplastic filament is melted and deposited layer-by-layer through a heated nozzle.	Facilitates the conversion of APIs into amorphous forms, significantly improving the bioavailability of BCS Class II and IV drugs.	High processing temperatures (150°C to 250°C) can cause thermal degradation of thermolabile APIs.
Semi-Solid Extrusion (SSE)	Extrusion of drug-loaded pastes or gels at or near room temperature using pneumatic or	Ideal for heat-labile compounds such as peptides and biological drugs due to gentle	Requires time-consuming curing or drying stages, which may lead to shrinkage or dimensional

	mechanical pressure.	processing conditions.	inaccuracies.
Selective Laser Sintering (SLS)	A high-powered laser selectively fuses powder particles together in a powder-bed fusion process.	Capable of producing highly porous structures that disintegrate quickly; achieves amorphization in a single step.	The high local heat of the laser poses risks of thermal and oxidative degradation of the material.
Vat Photopolymerization (SLA/DLP)	Curing of liquid photosensitive resins using a UV laser or light source.	Provides the finest spatial resolution (up to 25 μm), allowing for complex geometries and custom implants.	Limited availability of biocompatible resins and the risk of residual toxic monomers remaining in the dosage form.

Selective Laser Sintering (SLS) is a type of powder-bed fusion technology where no filaments or binders are used but rather a high-powered laser is used to selectively fuse powder particles together. A laser is used to trace a particular pattern onto a powder bed, and a new layer of powder is added to the top with each sintering[19]. The combination of SLS has the capability of producing highly porous structures that are highly disintegrable and dissolvable which are often hard to attain using the conventional compression techniques. In addition, amorphous conversion of the drug can be achieved in a single step by using the combined heat and laser energy. Nevertheless, the high local heat of the laser poses a threat of thermal and oxidative degradation, and laser intensity and scan rate are critical CPPs needed to validate. Sufficient validation of SLS must also be performed by monitoring the build chamber and bed temperatures closely so that the sintered material does not warp, and the entire batch of sintered material is evenly sintered.

The use of vat photopolymerization, namely Stereolithography (SLA) and Digital Light Processing (DLP) has the finest spatial resolution of all existing pharmaceutical 3DP modalities, some systems being as fine as 25 m. Such techniques develop dosage forms through the curing of liquid photosensitive resins with the help of a UV laser or light source. The complex geometries and smooth surface finishes made possible through SLA can be used to produce complex combinations of drugs (polypills) or custom implants to meet patient-specific anatomy needs. Nonetheless, regulatory and safety obstacles are major limiting factors of the clinical integration of SLA. The supply of biocompatible, FDA-approved photosensitive resins is limited and the danger of the leftover toxic monomers being left in the end dosage form because the polymerization process is not complete is a

significant validation issue. To verify SLA processes, it is then necessary to include stringent post-curing checks and solvent washing procedures so that all the unreacted monomers are eliminated and that the end product is non-toxic.

A clear separation of the duties is the key to the successful validation of these technical modalities in a decentralized "Hub-and-Spoke" model. This architecture has a centralized Hub (usually a pharmaceutical manufacturer) that controls the integrity of the feedstock intermediates- the pharma-inks - that are conducting the complicated chemical assays and stability testing needed to filaments or pastes. The decentralized "Spokes" (like the hospital pharmacies) then concentrate on the process validation of the 3D printer per se, that the physical characteristics of every printlet correspond to the digital prescription[20]. The model also reduces the quality assurance workload at the bedside by relying on non-destructive Process Analytical Technology (PAT) instruments, including in-line Near-Infrared (NIR) and Raman spectroscopy, to measure drug load and real-time detect solid-state forms. Uniting these technical modalities with powerful digital twins and blockchain-protected "digital threads," the industry can enter the future where personalized medicines are being manufactured with the same efficiency and safety as the mass-produced tablets.

4. Diagnostic and Experimental Methods: The Process Analytical Technology (PAT):

Clinical translation of three-dimensional printing (3DP) and decentralized manufacturing (DM) will require a fundamental change in the way pharmaceutical quality is determined. In the past, quality assurance (QA) has been based on the paradigm of quality-by-inspection, which involves producing and testing a set number of conformance batches and comparing them against established acceptance criteria through the use of destructive testing. Nevertheless, the latter model cannot be used within the traditional context of a patient-centric point-of-care (POC) manufacturing, in which small-batch or even single-unit point-of-care (POC) printlets (3D-printed tablets) are produced and delivered to the patient at the point of care. Process Analytical Technology (PAT) is the so-called sensory apparatus of decentralized quality control in this context, which makes it possible to verify dosage forms non-destructively and in real-time to provide patient safety and therapeutic effectiveness.

4.1 Why Traditional Analytics do not Work in Decentralized Environment.

The standard techniques of conventional characterization, like the High-Performance Liquid Chromatography (HPLC), and the Ultraviolet-Visible (UV-Vis) spectrophotometry, have been decades long gold standards of tracking content uniformity and amount of dose of solid oral drug products. Although they are accurate, these approaches have significant drawbacks that make them infeasible in a clinical or a decentralized setting. First, they are destructive in nature; before being analyzed, the tablets need to be disintegrated and dissolved in solvents, which practically destroys the personalized medication that goes to the patient. Second, they are expensive and lengthy, necessitating a lot of sample preparation, long elution times, and highly trained staff-luxuries not possible in a busy hospital pharmacy or bedside clinical environment[21].

4.2 Near-Infrared (NIR) Spectroscopy: Verification of Real-Time Dose.

The near-infrared (NIR) spectroscopy is now one of the most promising PAT tools to use in 3DP because it is non-destructive, has a high turnover rate, and the ability to give comprehensive physicochemical information.

4.2.1 Case Study: Efavirenz Printlets In-line NIR.

The viability of real-time dose verification was presented in a pioneer study of the decentralized production of efavirenz printlets. Anti-HIV drug Efavirenz needs individualized dosing since it is metabolized by CYP2B6 enzyme, and genetic abnormalities in individuals may result in severe adverse effects or sub-therapeutic troughs. The pharma-ink (efavirenz-loaded granulates) was centrally synthesized by a manufacturing partner (Losan Pharma) and then delivered to a decentralized location (UCL School of Pharmacy) to be made finalized by Direct Powder Extrusion (DPE) 3D printing.

Calibration models have been created using Partial Least Squares (PLS) regression which has proven to be exceptionally performing:

Linearity (): 0.9833, which means that there is a very strong correlation between the drug content that is predicted and actual.

Accuracy (RMSE): 1.0662, demonstrating the model to assess drug load accurately on unknown data.

This combined software control of the printer and the NIR sensor enables faster throughput and real time batch release where each personalised unit is given the required dosage prior to being released to the patient.

4.3 Raman Spectroscopy: Monitoring Solid-State and Amorphous.

Although NIR is a great tool in quantifying doses, Raman spectroscopy provides a better resolution of solid-state forms and polymorphic transitions. This is essential to 3DP methods such as Selective Laser Sintering (SLS) and Fused Deposition Modeling (FDM) which apply thermal energy to transform crystalline drugs into Solid Amorphous Dispersions (SADs) to increase the bioavailability of poorly soluble BCS Class II and IV drugs.

4.3.1. Case Study: Itraconazole SLS Printing

One of the studies on the SLS 3DP of itraconazole (a BCS Class II drug) applied the Raman spectroscopy to predict the amorphous content with high accuracy. SLS uses a laser to bond powder particles selectively, which in many cases leads to the amorphization of the API. Since amorphous materials do not have a long-range structural order, their Raman peaks tend to be broader and lower than crystalline amorphous materials[22].

The analysis was constructed of a PLS regression model depending on Raman shift regions (6001800) to measure the extent of amorphous conversion. The findings were conclusive:

Linearity (): 0.998.

Precision (RMSEP): 0.63% and is far better than detection limits of the so-called gold standard techniques such as X-ray Powder Diffraction (XRPD), which is often not detectable unless it is greater than 4% crystallinity.

Raman spectroscopy, therefore, offers an important point-and-shoot methodology for pharmacists in hospitals to determine that a printed drug has attained the desired amorphous state, which is critical in determining that the drug will dissolve and be absorbed as intended[23].

4.4 Enabling Pharma 4.0: Closed-Loop Control and Digital Twins.

The realization of Pharma 4.0 is preconditioned by the integration of PAT sensors (NIR, Raman, and pressure sensors) into the 3DP workflow. Such tools become the source of real-time information on the process of "Digital Twins" - dynamic virtual copies of the real manufacturing process. A digital twin constantly works with PAT sensor data to reflect the printer behavior and make predictions of future quality of products.

The digital twin can process real-time PAT data, identify new trends or deviations (e.g., a drop in nozzle temperature) by the digital twin, and send corrective control signals to keep the process within the validated Design Space[24]. This proactive management shifts the focus of reactive management of deviation to proactive process steering that is critical in ensuring a steady quality of hundreds of decentralized manufacturing sites.

PAT plays a transformative role in decentralized 3DP. The industry can ensure personalised medicines are safe and effective at the point-of-care by substituting the destructive, slow analytical methods with the rapid, non-destructive methods in-line NIR and Raman spectroscopy[25].

5. Advances in Therapeutic and Translational: The Hub-and-Spoke Model and the MHRA 2025 Framework:

One of the fundamental prerequisites of the therapeutic translation of three-dimensional printing (3DP) out of the laboratory to the clinical practice is the creation of the strong and scalable supply chain architecture. The existing pharmaceutical production model in which a limited number of centralized plants deliver complete products to consumers worldwide is more and more seen as a barrier to the provision of very personalized or short shelf life drugs. To this, the Hub-and-Spoke model of supply chain has been the most sought-after model of decentralized manufacturing (DM). In this model, the complicated manufacturing licences and analytical infrastructure needed to produce quality-controlled feedstock intermediates referred to as pharma-inks is held in a centralized system referred to as the Hub, typically a pharmaceutical manufacturer or a big research hospital[26].

The Spokes, which is located at the point-of-care (POC) like hospital pharmacies, community clinics or mobile units, performs the final fabrication of the dosage form with approved 3D printers. This strategic separation of labor will greatly ease the quality assurance workload at the clinical site. Whereas the Hub is in charge of the most technically challenging chemical and regulatory tests, the Spoke is in charge with the process validation of the printer itself, to

assure that the physical critical quality attributes (CQAs), i.e., the size, weight, and integrity of the so-called printlet, is aligned with the digital prescription[27]. This model was successfully empirically tested in a landmark case study of the anti-HIV drug efavirenz. Efavirenz-loaded granulates in this work were placed under Good Manufacturing Practice (GMP) conditions by a centralized industrial partner (Losan Pharma) and shipped to a decentralized 3D printing (DPE) site to be fabricated by direct powder extrusion (DPE).

On July 23, 2025, the UK Medicines and Healthcare products Regulatory Agency (MHRA) finally adopted " The Human Medicines (Amendment) (Modular Manufacture and Point of Care) Regulations 2025" which was a historic milestone in this translational momentum. This pioneering law is the first legal framework in the world that is meant to specifically govern decentralized and point-of-care manufacturing. Before this legislation, human medicines legislation was mainly aimed at the so-called standard model of fixed factory-based locations, which discouraged innovation in POC therapy because the legal framework mandated that all individual manufacturing sites be named on a license. The 2025 frame eliminates these obstacles by proposing the idea of a Control Site hub and an active Point of Care (POC) Master File[28].

The clinical effect of this regulation and structural change is radical, especially of medicinal products highly personalized, or with extremely short shelf-lives. Some cell and gene therapies or cancer vaccines prepared by patient biopsies are considered advanced therapy medicinal products (ATMPs), which can have a shelf-life of merely minutes or hours. The time it took to transport these treatments between a factory and a patient under the centralized model frequently led to degradation of the treatment or lost treatment opportunity. The MHRA 2025 framework enables these breakthrough medicines to be prepared on-site, at the bedside of the patient or in mobile micro-factories, cutting months to a few days to wait[29]. Moreover, the Act is in favor of the NHS vision of virtual wards and hospital-at-home models, allowing advanced manufacturing devices, which can be remotely controlled to produce individualized medications in the home setting of the patient.

6. Quality Assurance and Validation Frameworks of Decentralized 3DP :

The shift of a centralized model of mass-production to the concept of decentralized manufacturing (DM) at the point-of-care (POC) requires a complete redefinition of the quality assurance (QA) of pharmaceuticals. The classical QA paradigms are based on quality-by-inspection, in which batches of large size are manufactured and then the end-products are destroyed, in order to verify that they meet the specifications that were set beforehand. The impossibility of analyzing the end product makes this model incompatible with the unit or small-batch production of personalized 3D-printed medicines, which is the reality of this production type. To address this gap, the frameworks of validation will have to change to Quality-by-Design (QbD) and the digital thread, where the advanced technologies Process Analytical Technology (PAT), Digital Twins, and blockchain can be used to make sure the quality is a natural result of a controlled process instead of a stop point[30].

Quality-by-Design acts as the science to prove the decentralized processes of 3D printing. QbD workflow starts with the definition of the Quality Target Product Profile (QTPP), which is a description of the critical safety and efficacy properties of the dosage form to a particular patient, e.g., a particular dose strength, release profile or geometry. Based on this profile, Critical Quality Attributes (CQAs) are observed-physical, chemical or performance properties that should not exceed specified limits. CQAs in 3DP normally comprise of mass uniformity, content uniformity, structural fidelity and the solid-state form of the drug-polymer matrix. This is followed by validation of the Design Space which is a multidimensional combination of Critical Process Parameters (CPPs) which are nozzle temperature, printing speed and infill density that have been proven to give confidence of quality[31]. With these relationships established through multivariate experimentation, even in the production of highly customized units, decentralized sites are able to sustain a state of control.

Table 2: Validation Framework for Quality Parameters (CPPs & CQAs)

Parameter Category	Specific Parameters and Attributes	Significance in Validation Framework
Critical Process Parameters (CPPs)	Nozzle temperature, printing speed, infill density, extrusion pressure, laser intensity, and scan rate.	These parameters must be maintained within a multidimensional Design Space to ensure consistent quality.
Critical Quality Attributes (CQAs)	Mass uniformity, content uniformity, structural fidelity, and solid-state form (amorphous/crystalline).	These properties are defined in the Quality Target Product Profile (QTPP) to ensure safety and efficacy for the patient.
In-Line PAT Monitoring	Real-time drug load (NIR) and solid-state transitions (Raman spectroscopy).	Enables Real-Time Release Testing (RTRT), allowing hospital pharmacists to verify a dose non-destructively before administration.
Digital Twin Integration	Predictive maintenance, virtual experimentation, and proactive fault detection.	Synchronizes real-time data to create a dynamic digital replica of the process, improving the entire validation lifecycle.
Data Integrity	Adherence to ALCOA+ principles (Attributable, Legible,	Ensures the digital thread between the clinical prescription and the final printlet

Standards	Contemporaneous, Original, Accurate, etc.).	is untampered and secure.

One of the foundation blocks of the Pharma 4.0 validation lifecycle is the integration of Digital Twin technology, which is a dynamic digital replica of the actual manufacturing process, synchronized in real-time using real-time data transfer. The Digital Twin lifecycle also improves process validation in three different phases. In Stage 1 (Process Design), the digital twins are used as prototypes (DTPs) that allow virtual experimentation. This enables the scientists to model a number of what-if scenarios and to search the design space without using costly pharma-inks or active ingredients. Stage 2 (Process Qualification) Digital Twin Instances (DTIs) assess how the process may be consistently replicated at a discrete decentralized location by leveraging the use of local environmental and printer data to forecast ranges of performance. Lastly, the digital twin changes QA into a proactive quality management system in Stage 3 (Continued Process Verification)[32].

The sensory apparatus of these digital frameworks are non-destructive PAT tools that support Real-Time Release Testing (RTRT) in clinical environments. Near-infrared (NIR) and Raman spectroscopy, handheld or in-line, have shown to be very efficient in determining the concentration of drugs and in authenticating the solid-state form of printlets without their destruction. As an example, in-line NIR has been found to determine drug content in efavirenz printlets with high accuracy (), and Raman spectroscopy has been found to determine amorphous content in itraconazole SLS printlets with high accuracy (). These devices enable hospital pharmacists to assure themselves that each of the personalized units is at the correct dose and structure before it is administered, which is basically a point and shoot approach to the clinical validation[33].

The nature of 3DP being a digitally-driven process, data integrity is a core value and must be supported by the ALCOA+ principles: Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available. The integrity of data throughout the lifecycle of data (CAD design to final fabrication) is important in ensuring the safety and effectiveness of pharmaceutical products. This involves proven data collection systems and safer transmission protocols in a decentralized environment, which will avoid manipulation or loss of data[34].

The regulatory framework of MHRA 2025 in the UK offers the legal framework that is needed to execute such advanced validation models. The legislation enables a flexible healthcare environment, where with an introduction of the concept of a Control Site hub which manages a number of Spokes via dynamic Point of Care (POC) Master File, adding or removing sites without complete re-licensing is possible. This Hub-and-Spoke architecture will be used to put the sophisticated chemical testing in the center (the hub), and the spokes will be dedicated to the process validation of the validated printers with PAT and digital

twins. This strategic synthesis of QbD, digital twin-enabled monitoring, ALCOA+ data standards and blockchain security forms a roadmap of the safe, sustainable, and regulated clinical integration of 3D-printed personalized medicines[35]. The winning of this evolution depends on the possibility to demonstrate that the customization does not reduce the high quality of safety and consistency required in the modern pharmaceutical production.

7. Biological, Clinical and Outcome based Variations:

The basic reason why three-dimensional printing (3DP) should be implemented into the pharmaceutical setting is the understanding that the standardized approach of mass-production, which is packaged and made in one size, is biologically unsustainable. Decades of standardized dosage forms have been developed with fixed strengths based on average population response as seen in clinical trials a strategy that inherently fails to consider the dramatic inter-individual variability in genetic makeup, age, body mass, and disease pathology. Such a deficiency in personalization commonly leads to poor therapeutic results or adverse drug reactions (ADRs) in large groups of patients. Through 3D printing, clinicians can control the dose, geometry and release kinetics so that they can tailor the dosage to match the physiological and genetic profile of a single patient[36].

7.1 Precision Dosing and Pharmacogenomics.

The previous research of the effects of genetic variation on the individual response to drug use, known as pharmacogenomics, is a pillar of personalized medicine. Most drugs are broken down by certain enzymes, including the cytochrome P450 system, in which genetic polymorphisms may result in gigantic changes in drug exposure. The main clinical case is the antiretroviral drug efavirenz that is processed by the enzyme CYP2B6. Patients with some CYP2B6 genetic variations are prone to greater adverse effects because of poor metabolism, and others might develop sub-therapeutic troughs, which cause viral resistance. In such patients 3DP provides a means to manufacture accurate, customized doses, like the efavirenz-impregnated "printlets" tested in recent decentralized manufacturing simulations, which avoid the toxic peaks found with fixed doses of 600 mg daily[37]. With genetic testing, clinicians can send the digital prescription information to a 3D printer directly, thus providing the correct drug in the correct amount since it is based on molecular evidence, rather than population averages.

7.2 Vulnerable Populations: Pediatric and Geriatric Excellence

This clinical imperative of personalization is most severe in vulnerable groups whereby standard solid oral dosage preparations are often not available in the right amounts. The need to adjust doses depending on age and surface area is a common requirement of pediatric medicine, resulting in risky practices of tablet splitting or use of liquid formulations. Nevertheless, liquid medications are linked with errors in dosing, including mixing syringe marks or miscounting drops[38].

7.3 Differences by Sex and Physiological Consequences.

Differences in body weight, hormone levels, and genetic expression can have a tremendous impact on clinical outcomes of male and female patients, but these are rarely taken into consideration when it comes to centralized manufacturing. It has been shown that in certain clinical situations, the occurrence of adverse effects because of untailored therapy is up to 7585 percent. In the case of drugs with a small therapeutic index (e.g. warfarin or some cancer therapies), small changes in dosage can be disastrous. The dosage can be fine-tuned using 3DP to be dependent on the sex-specific metabolism rate and pharmacokinetics of a particular patient, which will save billions of healthcare dollars through avoidance of hospitalization in ADR. In addition, geometry and internal architecture (infill density or surface-areas-volume ratio) can be customized, offering a design-based way to regulate dissolution profiles, so that the drug will work best in the unique gastrointestinal conditions of the particular patient[39].

7.4 Clinical Practice Improvements based on outcome.

Decentralized 3DP has therapeutic potential, but not just to the physical product itself but to the quality of care in general. Point-of-care (POC) on-demand fabrication decreases the lead time of specialized therapies, especially of drugs with low shelf-lives or of those active against orphan diseases[40]. This change is aided by the creation of regulatory frameworks, including the UK MHRA 2025 regulations, which makes it possible to prepare breakthrough treatments, such as 3D-printed treatments or cell therapies, at a bedside. This responsiveness can be used in the NHS virtual ward and the hospital-at-home models, which provide patients with personalised care in the local communities.

8. Limitations, Risks, Future Direction:

The adoption of three-dimensional printing (3DP) in the pharmaceutical industry, though revolutionary, presents a multi-faceted set of technical, legal, and security issues that need to be resolved to achieve long-term sustainability of clinical implementation in 2026 and beyond[41]. With manufacturing no longer being centralized and high-throughput but decentralized and linked to the internet through clinical locations, the industry needs to be shunned off the traditional risk management paradigms, and adopt a holistic paradigm of digital security, shared liability models, and advanced computational frontiers.

8.1 Cybersecurity and the Threat of Digital Sabotage

Being a digital process, 3DP is particularly susceptible to cybersecurity attacks that may compromise patient safety and data integrity. The digital thread, the sequence between prescription given by a physician to the final printed drug, depends on three main types of files: CAD, STL, and G-code, all of which can be easily changed deliberately or accidentally[42]. Remote sabotage is an extremely risky issue, in which malicious parties may gain access to the internet-controlling software to alter a production design under the pretext of secretly doing so. A single minute deviation in G-code instructions can change the internal structure or spatial arrangement of the active pharmaceutical ingredient (API), creating a product with a different appearance, but with a pharmacologically harmful or toxic effect.

Moreover, weaknesses in 3D printer software and controller software can be used to introduce changes to printing characteristics covertly, including nozzle temperature or infill density, which directly influence the dosage form structural integrity and release kinetics. What is especially pernicious about these attacks is that they might lead to the occurrence of so-called hidden defects that can be identified only through the use of simple visual inspection[43]. To prevent such risks, decentralised manufacturing should follow the ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, and Available) principles and have effective digital safeguarding measures.

8.2 Decentralized Models Liability Conundrum.

The move towards decentralized manufacturing (DM) confuses the classic boundaries of responsibility in the pharmaceutical supply chain. With the traditional mass-production system, only the pharmaceutical manufacturer is responsible of safety and quality of the drug product. The "Hub-and-Spoke" model however entails several stakeholders, such as the drug formulator (Hub), equipment and software supplier, and the pharmacist or clinician at the point-of-care (Spoke). In case of a safety issue with a 3D-printed medication, it becomes a major legal and ethical challenge to attribute responsibility[44].

Legal systems such as the UK Medicines and Healthcare products Regulatory Agency (MHRA) 2025 regulations are the first steps to ending this uncertainty by defining the model of the Control Site hub. In this regime, the entire decentralized system is supervised by one control site and is the only name that appears on the manufacturing license. This site is charged with the responsibility of guaranteeing product quality in all manufacturing spokes and hence regulatory responsibility is centralized and the flexibility of POC treatments required. The international harmonization of liability standards is a key issue that needs to be addressed in order to have a global implementation despite these developments[45].

8.3 Technical and Material Constraints.

In addition to the digital and legal threats, 3DP constantly experiences technical constraints in the form of material supply and the speed of the process. Most pharmaceutical grade excipients in conventional manufacturing cannot be used in 3DP modalities; e.g. extrusion-based processes such as FDM require thermoplastic polymers that can resist high-processing temperatures (to) which can easily degrade thermolabile APIs. Also, medicines printed in 3D typically need secondary operations, like curing, drying, or depowdering, which may increase the cost and complexity of the production process and affect the porosity and dissolution characteristics of the final product[46].

8.4 Future Horizons: Industry 5.0 and High-order Compute.

The future of customized drugs resides in the nexus of additive production and new values of Industry 5.0, which is human-centered and more thoroughly integrated into computation. A number of frontier technologies will transform the pharmaceutical validation and design during the next decade:

Quantum Computing: With the limits of classical computing, quantum computing promises to be able to solve complex molecular simulations and optimization problems at the level of atoms. This will enable the accurate modeling of drug-excipient interactions and protein folding, and will speed up the creation of new "pharma-inks" of intricate biologics[47].

Multi-Omics Integration: The combination of transcriptomic, proteomic, and metabolomic data with manufacturing Digital Twins is one of the key frontiers[48]. Using patient-specific omics-data to add to the 3DP workflow, clinicians can now optimize medications to the cellular physiology and metabolic profile of a patient more precisely than ever.

Dark Factories and Autonomous GMP: The vision of the dark factory, with complete autonomy, digital-twin-controlled manufacturing systems that have minimal human intervention, is the final embodiment of Pharma 4.0/5.0. These systems would rely on AI and closed-loop PAT control to keep the fabrication process in a continuous state of control, possibly removing human error[49].

NHS "Virtual Wards" and At-Home Printing: The framework of MHRA in the UK already facilitates the idea of the so-called hospital-at-home and the virtual ward. In the short term, advanced manufacturing technologies might be remotely operated to produce customized therapies directly at home in a patient, and this would greatly improve the health care system.

To sum up, the way towards the large-scale clinical use of 3DP-printed personalized medicines must be a balanced one that would involve both the revolutionary possibilities and the serious threats. Although the problem of cybersecurity threats and the lack of liability is a significant challenge, the combination of blockchain-protected digital threads, Quality-by-Design (QbD) models, and Digital Twin technology offers a solid approach to the provision of a secure and reliable environment in the context of decentralization[50].

9. Conclusion:

The pharmaceutical sector has entered a turning point, which is a departure point of a 100-year-old paradigm of centralised mass production into an agile, patient-centric system that is based on three-dimensional printing (3D printing) and decentralised manufacturing (DM). As this review has critically shown, the one-size-fits-all medicine is no longer biologically or ethically viable in a world characterized by the genomic accuracy and molecular diagnostics. The most promising opportunity to improve patient safety and therapeutic outcomes since the emergence of industrial tableting is the convergence of additive manufacturing with point-of-care (POC) delivery.

The technological maturity of 3 DP modalities, most especially of Fused Deposition Modelling (FDM), Semi-Solid Extrusion (SSE), and Selective Laser Sintering (SLS), has shifted the technology into the stage of potential clinical fabrication. FDM and SLS have shown a distinct ability to promote amorphous solid dispersions with a substantial enhancement of bioavailability of BCS Class II and IV drugs.

The Quality-by-Design, non-destructive Process Analytical Technology, and Digital Twin technology strategic synthesis offers a roadmap to the safe and sustainable execution of 3D-

printed medicines. The shift out of the isolated pilot studies to an actual regulated clinical reality is no longer a technological hype but a necessity of translation. With the help of the decentralised mandate and the strong validation systems suggested in this review, the pharmaceutical industry will be able to eventually stop substituting the outdated one-size-fits-all tablet with a genuinely personalised course of therapy.

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