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QUALITY ASSURANCE AND NON-DESTRUCTIVE ANALYTICAL VERIFICATION OF 3D-PRINTED PHARMACEUTICAL DOSAGE FORMS: A CRITICAL REVIEW OF TECHNOLOGIES, CONTROL STRATEGIES AND REGULATORY READINESS

Purva Kalavadiya*[1], Aeshvi Vaghasiya[1], Bhavik Jani[2], Kushal Parekh[2], Pratik Vediya[2], Udit Trivedi[2], Ravi Ajudia[3]

[1]Student, [2]Assistant Professor, [3]Associate Professor

School of Pharmacy, RK University, Rajkot, Gujarat, India.

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***Corresponding Author: Purva Kalavadiya**

Student, School of Pharmacy, RK University, Rajkot, Gujarat, India.

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ABSTRACT

Three-dimensional printing (3DP) allows dose, geometry and internal architecture to be set digitally, which makes it attractive for small-batch, paediatric and patient-specific medicines. The same flexibility complicates quality assurance: configurations differ, batches may be tiny, and the conventional tests that confirm potency, uniformity and release usually destroy the unit examined. This review examines how printed dosage forms can be verified without consuming them. We set out the quality risks of the main printing platforms and link them to critical quality attributes, material attributes and process parameters. Near-infrared and Raman spectroscopy, chemical imaging, X-ray micro-computed tomography, terahertz imaging, optical coherence tomography, profilometry, machine vision and acoustic methods are compared according to what each actually measures, how directly it measures it and what evidence currently supports its use in printed products. The literature shows that spectroscopic dose verification and structural imaging of printlets are technically feasible. Most demonstrations, however, rely on a single formulation, a single printer and modest sample numbers, and model transfer, long-term robustness and false-acceptance rates are rarely reported. No single technique covers chemical, structural and performance attributes together. We therefore propose a staged, risk-based verification framework that combines controlled digital design files, feedstock and printer monitoring, rapid non-destructive screening, conventional reference testing and lifecycle management of analytical models, aligned with ICH Q8–Q14. Real-time release of printed medicines is a realistic long-term goal, but it will depend on validated links between measured signals and patient-relevant quality attributes rather than on instrumentation alone.

KEYWORDS: Additive Manufacturing; Printlets; Personalised Medicine; Process Analytical Technology; Near-Infrared Spectroscopy; Raman Spectroscopy; Micro-Computed Tomography; Quality By Design; Real-Time Release Testing.

Abbreviations

API: Active pharmaceutical ingredient

CAD: Computer-aided design

CMA: Critical material attribute

CPP: Critical process parameter

CQA: Critical quality attribute

DLP: Digital light processing

DoE: Design of experiments

DPE: Direct powder extrusion

EMA: European Medicines Agency

FDA: United States Food and Drug Administration

FDM: Fused deposition modelling

FMEA: Failure mode and effects analysis

ICH: International Council for Harmonisation

micro-CT: X-ray micro-computed tomography

MHRA: Medicines and Healthcare products Regulatory Agency

NIR: Near-infrared

OCT: Optical coherence tomography

PAT: Process analytical technology

PLS: Partial least squares

QbD: Quality by design

QC: Quality control

QTPP: Quality target product profile

RTRT: Real-time release testing

SLA: Stereolithography

SLS: Selective laser sintering

SSE: Semi-solid extrusion

THz: Terahertz

3DP: Three-dimensional printing

1. INTRODUCTION

1.1 Printing as a pharmaceutical manufacturing process

Additive manufacturing builds an object layer by layer from a digital model rather than shaping it by compression, moulding or subtraction. In pharmaceutics, the feedstock may be a drug-loaded filament, a paste, a powder bed with a liquid binder, a drug-containing ink or a photocurable resin, and the product may be a tablet (often called a printlet), an orodispersible film, an implant, a multiparticulate or another dosage form [1–3]. The technology was developed in engineering for rapid prototyping [4], and its use for drug delivery was explored from the mid-1990s onwards, first with powder-bed systems that could place drug and binder at defined positions within a matrix [5–7].

The field changed in 2015, when the United States Food and Drug Administration (FDA) approved Spritam® (levetiracetam), a highly porous, rapidly dispersing tablet made with a powder-bed process [8]. The approval showed that a printed medicine could pass through a conventional drug-approval pathway when product and process were supported by adequate evidence. It did not create a general route for every printing platform, and it said little about personalised or point-of-care production. In the decade since, desktop fused deposition modelling (FDM) [9], semi-solid extrusion (SSE) [10], selective laser sintering (SLS) [11], stereolithography [12] and several other approaches have been adapted to medicines, and the first clinical studies of printed formulations prepared in hospital settings have been reported [13,14].

What distinguishes printing from tablet compression is that geometry becomes a formulation variable. Infill density, shell thickness, layer height, lattice design and the placement of internal channels all influence mass, porosity, surface area-to-volume ratio, mechanical strength and drug release [15–17]. Multiple drugs can be placed in separate compartments with different release profiles [18,19], and dose can, in principle, be changed by editing a file rather than by making new tooling. These features explain the interest in printing for paediatric dosing, rare diseases, clinical-trial supplies and decentralised manufacture [20–22].

1.2 From feasibility to controlled manufacture

Early publications mostly asked whether a drug-containing object could be printed and whether its release could be tuned. Recent work asks harder questions: whether the dose in each unit can be verified, whether the product is stable, and whether a process can repeatedly make units that meet a specification [14,23,24]. This shift matters because a well-formed printlet is not necessarily a good medicine. A unit can look correct and still contain the wrong amount of drug, an altered solid form, degradation products from heat or light, or internal voids that change its dissolution. Printing therefore has to meet the same expectations of identity, strength, purity, performance and stability that apply to any other medicine, together with some new requirements for control of digital design files, printer software and data.

A further complication is that the quality question is no longer confined to the materials and the machine. The design file, the slicing parameters that convert it into a toolpath, the printer firmware

and the post-processing conditions together define the product. A version error in a design file can produce a perfectly printed unit with the wrong strength. Traceability from prescription or batch instruction to approved file, material lots, printer, operator and analytical record is therefore part of product quality, not an administrative extra [25,26].

1.3 Personalisation and its quality implications

Patient-specific manufacture is most useful where a fixed commercial strength does not meet an individual need: dose titration in children, narrow-therapeutic-index drugs, adults who cannot swallow conventional tablets, and patients taking several medicines that could be combined in one unit [19–21]. The clinical decision about the dose remains with the prescriber. The printer offers a way to make that dose, but it does not decide what the dose should be.

Personalisation shifts part of the quality burden from the factory to the information chain. The prescription has to be translated into an approved design, the correct material lot has to be loaded, and the record has to show that what was printed matches what was ordered. Independent checks matter because a wrong file or a wrong strength produces a unit that is physically well formed but clinically incorrect. A workable system defines in advance which variables may change without further evaluation. For example, a qualified family of strengths might allow dimensions to be scaled within a stated range while formulation and process stay fixed. It also defines which changes, such as a new polymer ratio, infill pattern or release architecture, require new comparative evidence. A method validated for one strength or shape should not be assumed valid for another [14,23].

1.4 Why non-destructive verification matters

Assay, content uniformity, dissolution and mechanical tests remain the reference methods for solid dosage forms. Almost all of them consume or alter the unit tested. That is acceptable when thousands of identical tablets are made and a statistical sample can represent the batch. It becomes a problem when a batch consists of a few dozen units, when every unit may differ in strength or shape, or when units are made for a named patient in a hospital pharmacy. Destroying a meaningful fraction of such a batch for testing is wasteful, and a small sample may miss sporadic defects such as a partial nozzle blockage or a brief feed interruption.

Non-destructive techniques offer a way out. Near-infrared (NIR) and Raman spectroscopy can estimate drug content or solid-state form within seconds [27,28]. X-ray micro-computed tomography (micro-CT) and terahertz imaging can reveal internal structure [29]. Machine vision can check geometry and visible defects on every unit [30]. Each of these methods, however, measures something specific and usually indirect. A spectral model predicts content from a calibration; it does not detect a crack. An image can show a void; it says nothing about potency. Whether a non-destructive result can support a quality decision depends on how well the measured signal has been linked to the attribute of interest and on how thoroughly the method has been validated for its intended use [31,32].

1.5 Scope and aim of this review

Several reviews have described printing technologies and their pharmaceutical applications [1,2,14,33,34]. Fewer have examined quality assurance as a system that links digital design, material and process understanding, conventional quality control (QC), non-destructive analytics, process analytical technology (PAT), quality by design (QbD) and regulatory expectations. The aim of this review is to provide that synthesis. Specifically, we (i) summarise the quality risks associated with the main pharmaceutical printing platforms; (ii) describe the physical, chemical and performance-related critical quality attributes (CQAs) of printed dosage forms and their links to material attributes and process parameters; (iii) evaluate non-destructive analytical and imaging techniques according to the attribute measured, directness of measurement and maturity of evidence; (iv) discuss PAT, real-time monitoring and real-time release testing (RTRT); (v) outline validation and regulatory considerations; and (vi) propose an integrated, risk-based verification framework and an agenda for future research.

2. REVIEW METHODOLOGY

This article is a structured narrative review. Literature was identified through Google Scholar, PubMed/PubMed Central, Scopus and publisher platforms, supplemented by the official websites of the FDA, the European Medicines Agency (EMA), the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the International Council for Harmonisation (ICH). Searches combined technology terms ("3D printing", "additive manufacturing", "printlet", "fused deposition modelling", "semi-solid extrusion", "selective laser sintering", "stereolithography", "binder jetting", "inkjet printing") with quality and analytical terms ("quality control", "non-destructive", "near-infrared", "Raman", "chemical imaging", "micro-CT", "terahertz", "optical coherence tomography", "machine vision", "process analytical technology", "quality by design", "real-time release", "validation") using Boolean operators. Searches covered publications from 1990 up to October 2026, when the final search was run. Reference lists of key reviews were screened to find further primary studies.

Sources were included if they dealt with pharmaceutical dosage forms produced by printing and addressed quality attributes, analytical or imaging methods, process monitoring, risk management, validation or regulation. Studies on non-pharmaceutical printing were included only when they offered a transferable principle, for example in-situ monitoring of extrusion. Official guidance and pharmacopoeial texts were used for regulatory statements, and peer-reviewed primary studies were preferred for technical claims. Device-specific guidance was cited only for general engineering concepts and is not presented here as drug-product regulation.

For each relevant study we noted the printing platform, dosage form, attribute measured, analytical principle, reference method, sample numbers, validation approach and the decision the method was intended to support. Because the aim was a conceptual and critical synthesis rather than an estimate of effect sizes, no meta-analysis or formal risk-of-bias scoring was performed, and no PRISMA-style

counts are reported. Findings were grouped thematically and compared in summary tables. Proof-of-concept results were interpreted as evidence of feasibility, not of routine manufacturing readiness.

3. Printing platforms and their quality risks

ISO/ASTM 52900 groups additive manufacturing into seven process categories, of which material extrusion, powder-bed fusion, binder jetting, material jetting and vat photopolymerisation have been most explored for medicines [35,36]. Each category imposes a different mix of thermal, mechanical, solvent and optical stress on the formulation, and each fails in its own way. No platform is superior in general, and the control strategy has to be built around the failure modes of the platform actually used. Table 1 summarises the principal risks and the verification tools most suited to them.

3.1 Fused deposition modelling

In FDM, a thermoplastic filament containing drug, polymer and often a plasticiser is fed through a heated nozzle and deposited along a programmed path [9,37]. Filaments are usually made beforehand by hot-melt extrusion, which is itself a manufacturing step with its own variability. Ponsar and colleagues showed that fluctuations during filament extrusion produced diameter and drug-content variation that carried through to the printed dosage forms [38]. Filament diameter, mechanical properties (a brittle filament snaps in the feeder; a soft one buckles), moisture content and drug distribution are therefore critical material attributes.

The main process risks are thermal. The API experiences heat twice, during filament extrusion and again in the nozzle, and the relevant exposure is the full thermal history, including residence time, rather than the nominal nozzle setpoint. Lower-temperature formulations have been developed to extend FDM to more heat-sensitive drugs [39,40]. Inconsistent extrusion alters road width, porosity and unit mass, and changes in infill or shell thickness can shift dissolution markedly even with an unchanged formulation [15,41]. Verification therefore needs to combine dimensional checks, unit mass, chemical measurement of drug content and, during development, structural imaging.

3.2 Semi-solid extrusion and pressure-assisted microsyringe printing

SSE deposits a paste, gel or other viscoelastic material through a syringe under pneumatic or mechanical pressure, and usually avoids high temperatures [10,42]. Rheology is central. If viscosity is too low, deposited lines spread and dimensional fidelity is lost; if it is too high, pressure becomes unstable and the nozzle may block. Drying or curing after printing can cause shrinkage, cracking and migration of drug or solvent. Suspended drug particles may settle in the syringe over time, producing a content gradient between the first and last units of a run, so the maximum holding time of the feedstock should be established and written into the batch record. SSE is the platform used in the first clinical study of automated printing of an amino-acid supplement for children with maple syrup urine disease, carried out in a hospital setting [13]. Pressure-assisted microsyringe printing applies the same principle at smaller volumes and shares the same risks of clogging and time-dependent viscosity change.

3.3 Direct powder extrusion

Direct powder extrusion (DPE) feeds a powder blend into a single-screw extruder mounted on the print head, removing the need for a separate filament [43,44]. This simplifies the workflow but shifts the burden of control to powder feeding. Bridging in the hopper, segregation and variable bulk density can produce transient changes in output. Start-up, refill and shutdown periods should be characterised separately from steady-state operation, and the control plan should state whether units printed during those periods need extra testing or should be rejected.

3.4 Binder jetting

Binder jetting spreads a thin layer of powder and selectively deposits a liquid binder to join particles; the process is repeated layer by layer and the unbound powder is removed afterwards [45,46]. The approved levetiracetam product was made in this way [8]. Powder flowability, particle size, layer uniformity, binder saturation, droplet size and drying conditions determine strength, porosity and residual solvent. High porosity is often deliberate because it allows rapid dispersion, so structural acceptance criteria must be referenced to the intended architecture rather than to a generic goal of minimising voids. The resulting units can be friable, which makes mechanical integrity and handling during packaging important attributes.

3.5 Inkjet printing

Inkjet systems place picolitre-scale droplets of drug-containing ink onto a substrate such as a film, a porous carrier or a powder bed [47,48]. Viscosity, surface tension, solvent volatility, nozzle health and substrate wetting govern deposition. Blocked nozzles, satellite droplets and misplaced drops can change local dose without any visible change in the overall unit. Optical monitoring can check placement, but establishing the amount and distribution of drug requires chemical measurement. Raman chemical imaging has been used to visualise and quantify inkjet-printed APIs on different substrates [49], and spectroscopic verification of drug printed onto contact lenses has also been reported [50].

3.6 Selective laser sintering

SLS uses a laser to fuse selected regions of a powder bed, without a solvent and without a separate filament [11,51]. Laser power, scan speed, hatch spacing, layer thickness, bed temperature and the absorptivity of the powder (often adjusted with a small amount of colourant) determine the degree of sintering, which controls density, porosity and drug release. Local heating can also convert crystalline drug to an amorphous form, a change that may be desirable for solubility but needs to be measured and kept stable. Trenfield and colleagues used NIR and Raman spectroscopy to predict the solid-state form of drug in SLS printlets [28], and NIR to predict density and drug release [52]. If unused powder is recycled, a written policy should define storage, testing and maximum reuse, because thermal history can alter subsequent sintering.

3.7 Vat photopolymerisation: stereolithography, digital light processing and volumetric printing

Stereolithography (SLA) and digital light processing (DLP) cure a liquid resin containing monomer, photoinitiator and drug with a scanned laser or a projected light pattern [12,53,54]. These methods give high resolution and allow complex multi-compartment designs [19]. The specific risks are incomplete conversion, residual monomer and photoinitiator, and light-induced or chemical interaction between drug and resin. In one case a drug reacted with the photopolymer during printing, a finding that would not have been predicted from the nominal formulation [55]. Drug particles and pigments can scatter or absorb light, changing the effective exposure within each layer. A spectroscopic signal that confirms resin conversion does not confirm that the API is intact or present at the target concentration. Tomographic volumetric printing, which cures a whole object at once by projecting light patterns into a rotating vial, can produce printlets within seconds [56] but brings the same chemical questions.

3.8 Hybrid and emerging approaches

Hybrid workflows combine printing with conventional steps such as coating, capsule filling or compression. One industrial study described the design and qualification of a single-step "print and fill" capsule [57]. Wherever printed and conventional components meet, the interface itself becomes a potential failure point and should be included in the risk assessment.

Table 1. Principal pharmaceutical printing platforms, their dominant quality risks and the verification tools most suited to them.

Platform	Principle and feedstock	Key CMAs / CPPs	Dominant quality risks	Most useful verification tools
FDM [9,37,38]	Drug-loaded thermoplastic filament melted and extruded through a heated nozzle	Filament diameter, mechanics, moisture, drug distribution; nozzle temperature, speed, layer height, infill	Thermal degradation; filament variability carried into product; under-/over-extrusion; infill-dependent release	Unit mass, machine vision, NIR/Raman for dose, micro-CT in development
SSE / pressure-assisted microsyringe [10,42]	Paste or gel extruded under pressure at or near room temperature	Viscosity, yield stress, solids content; pressure, nozzle size, drying	Sedimentation and content drift over a run; shrinkage and cracking on drying; nozzle blockage	Mass and dimensions, NIR (moisture-aware), periodic assay across run
DPE [43,44]	Powder blend fed directly to a screw extruder on the print head	Particle size, flow, bulk density; screw speed, barrel temperature	Feeding instability; start-up and refill transients; thermal stress	Feed and torque monitoring, unit mass, spectroscopy on start-up units

Platform	Principle and feedstock	Key CMAs / CPPs	Dominant quality risks	Most useful verification tools
Binder jetting [8,45,46]	Liquid binder jetted onto successive powder layers	Powder flow, layer uniformity; binder saturation, droplet size, drying	Friability; residual solvent; uneven bonding; distinguishing designed porosity from defects	Machine vision of layers, mechanical tests, micro-CT, residual-solvent testing
Inkjet [47–49]	Drug-containing ink deposited as droplets on a substrate or powder bed	Ink viscosity, surface tension, volatility; droplet volume, frequency	Nozzle failure and misplaced drops causing local dose error; substrate interaction	Droplet imaging, Raman/NIR chemical imaging, reference assay
SLS [11,28,51]	Laser fuses selected regions of a powder bed	Powder absorptivity, particle size; laser power, scan speed, bed temperature	Variable sintering and density; amorphisation or degradation; powder reuse	NIR/Raman for solid state and density, micro-CT, dissolution
SLA / DLP / volumetric [12,53,55,56]	Photocurable resin containing drug cured by laser or projected light	Resin composition, photoinitiator, optical properties; exposure, post-cure	Incomplete cure; residual monomer and photoinitiator; drug–resin reaction; light-induced degradation	Dimensional imaging, extractables testing, stability-indicating assay; spectroscopy with caution

4. Quality attributes, material attributes and process parameters

4.1 Defining the printed product

A printed dosage form is defined by a formulation and a digital description. The computer-aided design (CAD) model sets external geometry and intended internal features, and the slicing software converts it into layers, toolpaths and machine instructions. Both should be treated as controlled elements of the product specification [58]. The approved record should identify the file, its revision and checksum, the software versions used, the printer models with which it is qualified and its approval status. Design review should state which features are functional, for example a lattice intended to speed liquid ingress, and which dimensions are critical.

This matters because, in printing, the line between a design feature and a defect is easy to blur. A void is not automatically a defect. A channel built into the design to accelerate disintegration is part of the product, whereas a void of the same size produced by an interrupted feed is a failure. Specifications should therefore describe what the unit should look like, which structural features are intended, how they are measured and what limits separate acceptable variation from failure.

4.2 Critical quality attributes

CQAs are physical, chemical, biological or microbiological properties that must lie within an appropriate limit, range or distribution to ensure product quality [58]. They should be derived from

the quality target product profile (QTPP) and the intended clinical use rather than copied from a generic list. For printed oral dosage forms they fall into three groups (Table 2).

Physical attributes include mass, dimensions, shape fidelity, surface texture, density, porosity, layer adhesion, mechanical strength, friability and appearance. Mass and dimensions are informative but indirect. A unit of correct mass may still have a non-uniform drug distribution, and correct external dimensions say nothing about internal defects.

Chemical attributes include identity, assay, content uniformity, degradation products, residual solvents or monomers, water content and solid-state form. Printing can create chemical gradients through sedimentation in SSE feedstock, uneven powder feeding, drift in droplet volume or migration during drying. Thermal or photochemical stress can create degradation products that would not arise during compression [40,55].

Performance attributes include disintegration, dissolution, release kinetics and stability over shelf life. In printed products these are sensitive to geometry. Surface area-to-volume ratio has been used to predict release across different tablet shapes [16], and designs that fragment without a disintegrant show how architecture can substitute for an excipient [59]. Structural measurements can act as surrogates for release only after an experimental relationship has been demonstrated and its limits defined [52].

Stability deserves separate mention. Printed units are often more porous, have a larger surface area or contain amorphous drug or plasticised polymer, all of which can make them more sensitive to moisture and temperature than compressed tablets of the same composition. Where drug has been amorphised by heat or laser energy, recrystallisation during storage may slow dissolution. Stability programmes should therefore include the attributes most likely to change, such as solid-state form, water content, mechanical strength and dissolution, and should test the packaging actually intended for supply. For units made on demand and used within days, the relevant shelf life may be short, but it still has to be supported by data.

Table 2. Critical quality attributes of printed oral dosage forms, conventional reference methods and candidate non-destructive approaches.

CQA	Why it matters in printing	Conventional reference method	Candidate non-destructive approach (status)
Identity	Wrong feedstock or mixed-up cartridge produces a well-formed but wrong product	Chromatography, spectroscopic identity test	NIR or Raman identity screening (well established in pharmaceutics generally)
Assay / dose	Dose is set by geometry and drug loading; extrusion or deposition errors change it	HPLC after extraction	Quantitative NIR/Raman with PLS calibration (demonstrated in printlets; needs product-specific validation) [27,60]

CQA	Why it matters in printing	Conventional reference method	Candidate non-destructive approach (status)
Content uniformity	Sedimentation, feed variation and droplet drift create unit-to-unit variation	Compendial uniformity of dosage units [61,62]	Every-unit spectroscopic prediction; chemical imaging for within-unit distribution [49,63]
Mass and dimensions	Indicate interrupted or excess deposition, warping and shrinkage	Balance, calipers	Machine vision, profilometry, in-line weighing (established for visible attributes)
Porosity and internal structure	Often functional and design-specific; voids or delamination may be defects	Mercury porosimetry, sectioning	Micro-CT, terahertz imaging (development and investigations) [29]
Solid-state form	Heat or laser energy can amorphise or change polymorphs	XRPD, DSC	Raman, NIR (demonstrated for SLS printlets) [28]
Mechanical integrity	Weak inter-layer bonding or high porosity cause breakage	Breaking force, friability	Acoustic methods (emerging); structural imaging as surrogate
Disintegration / dissolution	Highly sensitive to geometry, infill and bonding	Compendial apparatus [64]	Spectroscopic or structural surrogate models (early evidence) [52]
Impurities and residuals	Thermal and photochemical stress; residual monomer or solvent	Stability-indicating HPLC, GC	Generally not suitable for non-destructive measurement at present

4.3 Critical material attributes

Potential critical material attributes (CMAs) include API particle size, solid form and thermal stability; polymer grade and molecular weight; plasticiser content; filament diameter and mechanical behaviour; powder flow, bulk density and blend uniformity; paste viscosity and yield stress; ink viscosity and surface tension; water content; and, for light-based processes, optical absorbance and scattering. Not every attribute is critical in every process, and criticality should be justified by risk assessment and data. Supplier changes and lot-to-lot variability in excipients should be managed through specifications and change control. Machine-learning analysis of several hundred FDM formulations has shown that material properties can be used to predict printability [65], which shows how strongly feedstock behaviour governs process success.

4.4 Critical process parameters

Critical process parameters (CPPs) depend on the platform: nozzle and bed temperature, feed rate, print speed and layer height for FDM; pressure, nozzle diameter and drying conditions for SSE; screw speed and barrel temperature for DPE; binder saturation and layer thickness for binder jetting; droplet volume and firing frequency for inkjet; laser power, scan speed and hatch spacing for SLS; and exposure dose and post-cure time for vat photopolymerisation. Infill, shell thickness and orientation,

although set in software, behave as process parameters and should be controlled in the same way. Ambient temperature and humidity can matter, particularly for hygroscopic filaments and pastes. A setpoint alone does not guarantee a stable process if the feedstock or equipment drifts. Calibration, preventive maintenance, alarms and verification of software settings are part of the control of CPPs.

4.5 Causal links between CMAs, CPPs and CQAs

The value of the CMA–CPP–CQA framework is that it turns a long list of possible measurements into a set of causal hypotheses that can be tested. Consider an FDM process (Figure 1). Water absorbed by the filament lowers melt viscosity. Viscosity interacts with nozzle temperature and feed rate to determine how much material leaves the nozzle and how well each road fuses with the one below. These factors set road width, porosity and inter-layer bonding, which in turn influence unit mass, content uniformity, mechanical strength and dissolution. A comparable chain can be written for every platform. Risk assessment identifies the links that matter most, design of experiments (DoE) quantifies them, and the control strategy places measurements or controls at the points where they can prevent or detect failure.

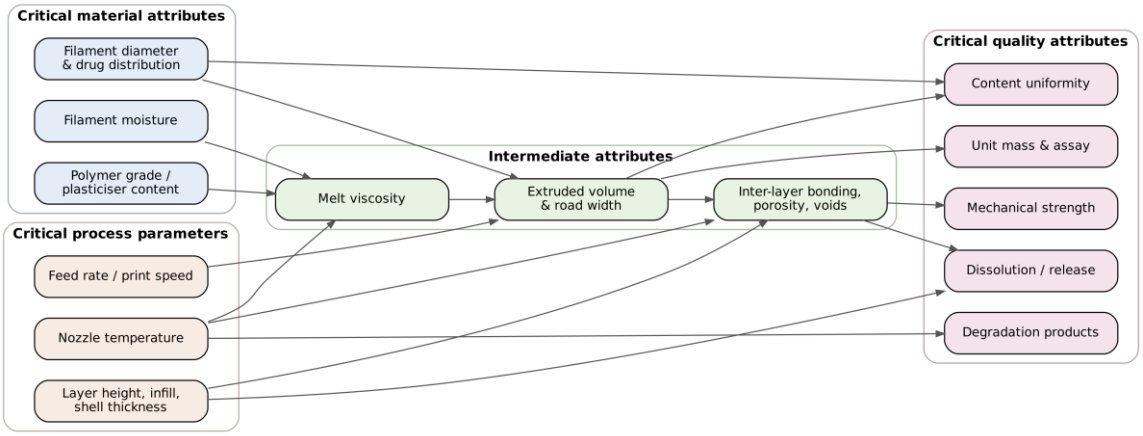


Figure 1. Example of causal links between critical material attributes, critical process parameters, intermediate structural attributes and critical quality attributes in fused deposition modelling. Arrows indicate influence; the diagram is illustrative and should be confirmed experimentally for each formulation and printer.

The same reasoning helps in investigations. Low unit mass suggests interrupted feeding. Acceptable mass with low assay points instead to non-uniform drug distribution. Cracking may result from drying stress, poor bonding or unsuitable rheology. These are hypotheses to test, not conclusions to draw from appearance.

5. Conventional quality control: role and limitations

Conventional QC remains indispensable. Chromatographic assay and content uniformity provide the reference measurements against which any non-destructive method must be calibrated [61,62].

Disintegration and dissolution are the accepted measures of in vitro performance [64]. Mass and dimension checks, crushing strength, friability, thermal analysis, X-ray powder diffraction and water determination complete the usual characterisation. During development the test panel is broader than at routine release, and stability-indicating methods are needed wherever thermal or photochemical stress is possible.

The limitations of these methods for printed products are practical rather than scientific. Most are destructive; several are slow; all depend on sampling. In a small or personalised batch, testing even a few units may consume a large fraction of the output, and a statistical sample may not capture a sporadic, short-lived defect. Mass is a useful screen but a poor surrogate for dose, because API concentration can vary independently of unit weight. Dimensional checks cannot rule out internal defects. Dissolution testing captures performance but cannot be applied to a unit that is later given to a patient.

These limitations justify complementary approaches. They do not make conventional testing obsolete. A realistic strategy uses reference methods to build and periodically confirm non-destructive calibrations, uses non-destructive methods to screen every unit or a much larger sample, and uses process monitoring to prevent defects in the first place.

6. Non-destructive analytical and imaging techniques

Non-destructive techniques differ in what they measure (chemical composition, solid state, structure or surface), how deeply they probe, their spatial resolution, their speed and their sensitivity to the formulation matrix. Choosing one should start from the CQA and the decision to be supported, not from the instrument available in the laboratory. If the concern is visible deformation, machine vision or profilometry may be sufficient. If it is dose, spectroscopy is the obvious candidate. If it is internal voids or delamination, three-dimensional imaging is needed. Table 3 compares the main options.

6.1 Near-infrared spectroscopy

NIR spectroscopy records overtone and combination bands, mainly of C–H, O–H and N–H bonds. Measurements take seconds, need no sample preparation and can be made through some packaging materials [66,67]. Because bands are broad and overlapping, quantitative work relies on multivariate calibration, most often partial least squares regression [68]. NIR is long established in pharmaceutical manufacturing for raw-material identification, blend monitoring and tablet assay, and both the FDA and EMA have issued guidance on developing and submitting NIR procedures [69–71].

For printed products, the most cited demonstration is a handheld "point-and-shoot" NIR method used to verify the dose of printlets non-destructively [27]. The same group extended the approach to units containing two drugs [60], to prediction of solid-state form in SLS printlets [28] and to prediction of density and drug release [52]. NIR chemical imaging has also been used to visualise drug distribution in printed dosage forms [63].

These studies establish feasibility, but they also show where the difficulties lie. NIR spectra respond to water, temperature, particle size, density and surface roughness as well as to composition, and printed units vary in all of these. A calibration built on one strength or geometry may not hold for another, and a model can learn an accidental correlation if concentration is confounded with batch, shape or moisture in the calibration set. Good practice therefore requires a calibration design that spans the expected variation, preprocessing choices that are documented and justified, an independent test set, reported bias and prediction error, and a rule for identifying spectra that fall outside the calibration domain [72,73]. Transfer to another instrument or site requires documented assessment, not an assumption of equivalence [74].

6.2 Raman spectroscopy

Raman spectroscopy measures inelastic light scattering and gives sharp, chemically specific bands, so it is often better than NIR at distinguishing one API from another or detecting polymorphic change [75,76]. Confocal and mapping configurations add spatial information. Raman has been used to quantify inkjet-printed drugs on different substrates [49] and, with NIR, to predict solid-state form in SLS printlets [28]. Its weaknesses are fluorescence from excipients or colourants, which can swamp the Raman signal; weak signals at low drug loading; possible heating by the laser; and, for point measurements, a small sampled volume that may not represent the whole unit. A detailed Raman map is not automatically representative of the dosage form, so the number and position of sampling points and the method of converting a map into a unit-level result need to be justified.

Neither technique is generally superior. NIR tends to suit rapid bulk measurement and moisture-sensitive attributes; Raman tends to suit chemical specificity and solid-state questions. The choice depends on the spectral features of the API and excipients, the required depth and throughput, and the intended use.

6.3 Chemical and hyperspectral imaging

Chemical imaging records a spectrum at every pixel, producing maps of drug and excipient distribution [77]. In printing, it can reveal whether drug is uniformly distributed across layers or concentrated in particular regions [49,63]. The price is a large data volume and a heavier analysis burden. Lighting, calibration, focus, surface texture, sample positioning, preprocessing and the choice of multivariate model all influence the result. Imaging is usually limited to the surface or near-surface region, so internal heterogeneity may not be seen. Quantitative mapping requires both spectral and spatial validation.

6.4 X-ray micro-computed tomography

Micro-CT reconstructs three-dimensional structure from a series of X-ray projections. It can quantify porosity, pore connectivity, wall thickness, cracks, inter-layer gaps and deviations from the CAD model [29,78]. For printed products, where internal architecture is often a designed functional feature, this is uniquely useful. Markl and colleagues used micro-CT together with terahertz pulsed imaging to compare printed structures with their intended designs and to characterise internal defects [29].

Micro-CT has limits that matter for routine use. Scan and reconstruction times are long relative to printing, equipment is costly, and results depend on voxel size, reconstruction algorithm and segmentation thresholds, all of which should be fixed or controlled. Contrast between drug and excipients is often poor, so micro-CT rarely provides potency information. It is best placed in development, for setting structural acceptance ranges, in method validation and in deviation investigations. Its findings should be tied to a decision, for example comparing measured void fraction with a justified range or triggering dissolution testing when a crack is detected.

6.5 Terahertz spectroscopy and imaging

Terahertz radiation penetrates many polymeric excipients and is sensitive to refractive-index changes at interfaces, which allows measurement of coating thickness, density and some solid-state properties [79]. In printed structures it has been used alongside micro-CT to examine internal features [29]. Strong absorption by water, sensitivity to geometry, specialised equipment and complex data interpretation limit its use at present to specialised development and investigational work.

6.6 Optical coherence tomography

Optical coherence tomography (OCT) uses low-coherence light to produce cross-sectional images of near-surface structure at micrometre resolution and high speed. In conventional manufacturing it has been evaluated for coating thickness and uniformity, often in comparison with terahertz imaging [80]. For printed dosage forms, OCT could assess surface layers, coatings and shallow defects, but penetration in strongly scattering or opaque materials is limited. Its role is structural rather than chemical.

6.7 Profilometry and machine vision

Laser profilometry and structured-light scanning measure surface height and can compare a printed unit with its digital model, detecting warping, sagging or under-extrusion. Machine vision uses cameras and image-analysis algorithms, increasingly including machine learning, to inspect shape, dimensions, colour and surface defects at production speed [30,81]. Both techniques are well suited to 100% inspection of visible attributes. Performance depends on lighting, focus, positioning, resolution and the defect types represented in the training or validation set. Models must be re-evaluated when geometry, colour or camera conditions change. Neither technique can detect internal or chemical defects, and a unit that passes optical inspection may still be sub-potent.

6.8 Acoustic and other emerging approaches

Ultrasonic and other acoustic methods probe mechanical properties and internal interfaces and could, in principle, detect delamination or density differences in printed units. Coupling, the small size and irregular shape of dosage forms, and attenuation in porous structures are practical obstacles, and evidence in printed medicines is still limited. Thermal imaging of the deposition zone, analysis of printer telemetry and sensor fusion, in which data from several sensors are combined in a single model, are being explored [81]. In metal and polymer additive manufacturing outside pharmacy, in-situ monitoring of melt pools, layer images and acoustic emission is well developed, and some of

these principles may transfer [82]. Combining sensors can cover more failure modes, but it also multiplies calibration, data-governance and model-maintenance work.

6.9 Comparative assessment

Three conclusions follow from the comparison. First, spectroscopic and imaging techniques are complementary. A structurally perfect unit may contain the wrong dose, and a chemically uniform unit may be cracked. Second, maturity should be judged by evidence for the specific application, not by the general reputation of a technology. NIR and Raman have the longest pharmaceutical track record, but each printed application still needs product-specific validation. Third, the published printing studies, although encouraging, usually involve one formulation, one printer, a limited range of strengths and laboratory-scale sample numbers. Robustness across material lots, instruments and time, and the rates of false acceptance and false rejection, are seldom reported.

Table 3. Comparison of non-destructive analytical and imaging techniques for printed dosage forms.

Technique	Information obtained	Speed	Main strengths	Main limitations	Maturity in printed products
NIR spectroscopy [27,67]	Dose, identity, moisture, density, solid state (via calibration)	Seconds	Fast; no preparation; handheld options; regulatory guidance exists	Indirect; sensitive to water, geometry and surface; calibration transfer	Several proof-of-concept and dose-verification studies
Raman spectroscopy [49,75]	Identity, dose, polymorphic form, distribution	Seconds to minutes	High chemical specificity; mapping possible	Fluorescence; weak signal at low loading; small sampled volume; laser heating	Proof of concept on several platforms
Chemical / hyperspectral imaging [63,77]	Spatial distribution of drug and excipients	Minutes	Visualises heterogeneity	Large data sets; mostly surface; complex validation	Development and research use
Micro-CT [29,78]	3D porosity, voids, cracks, layer gaps, deviation from CAD	Minutes to hours	Unique internal 3D information	Slow; costly; little chemical contrast; segmentation-dependent	Widely used in development; not routine release
Terahertz imaging [79]	Layer interfaces, density, coating thickness	Minutes	Penetrates many excipients; depth-resolved	Water absorption; geometry effects; specialised equipment	Limited studies

Technique	Information obtained	Speed	Main strengths	Main limitations	Maturity in printed products
OCT [80]	Near-surface cross-sections, coating layers	Fast	High resolution; potential in-line use	Shallow penetration in scattering materials; structural only	Not yet established for printlets
Profilometry / machine vision [30]	Shape, dimensions, surface defects, colour	Milliseconds to seconds	Suited to 100% inspection; automatable	Visible features only; re-validation when geometry or lighting changes	Demonstrated; readily implementable
Acoustic / ultrasound	Mechanical properties, interfaces	Seconds	Probes internal mechanics	Coupling; small, porous, irregular units	Emerging

7. Process analytical technology and real-time quality assurance

7.1 Concepts and measurement modes

PAT is a framework for designing, analysing and controlling manufacturing through timely measurement of critical quality and performance attributes of raw and in-process materials and processes [83]. Its purpose is to understand and control the process, not simply to place an analyser at the end of the line. Measurements may be in-line (the sensor sits in the process stream, for example a pressure transducer in an extrusion head), on-line (material is diverted to an analyser and may be returned), at-line (samples are removed and measured close to the process, for example with a handheld spectrometer) or off-line (in the laboratory). Each mode brings its own concerns: fouling, drift and missing data for in-line sensors; transport delay and representativeness for on-line systems; and handling, sample identification and frequency for at-line measurements.

7.2 Process signals available in printing

Printers already generate data that can serve as process signals: nozzle and bed temperatures, extrusion force or pressure, motor current, feed-rate encoders, laser power, chamber temperature and humidity, and layer images. In extrusion systems, a drop in pressure or a change in feed-motor load can flag a blockage or filament slip before a defective unit is completed. Ponsar and colleagues showed that variability in the upstream filament process propagates into printed products [38], which argues for monitoring the feedstock as well as the printer. A staged approach is sensible: identify a meaningful signal, show its relationship to a CQA, validate the measurement, set alarm limits, and test the operator or automated response with deliberately induced faults. Data that are collected but not linked to a decision do not constitute control.

7.3 Feedback control

When a monitoring system automatically adjusts printer settings, further controls are required. The permitted adjustment range, the software version, the validity checks on sensor input, the response to

missing data and the conditions that trigger a safe stop should all be defined in advance. Changes to the feedback algorithm should go through formal change control. Closed-loop control of pharmaceutical printing has been discussed more often than demonstrated, and validated examples are still needed.

7.4 Real-time release testing

RTRT is the ability to evaluate and ensure the quality of in-process or final product on the basis of process data, typically a validated combination of measured material attributes and process controls [58,84]. It is attractive for printed medicines because it could avoid destroying units. It requires, however, a demonstrated scientific relationship between what is measured and the CQAs that would otherwise be tested, a validated model with defined limits, and procedures for sensor failure. A spectrometer mounted on a printer does not, by itself, constitute RTRT. In the near term a hybrid release strategy is more realistic, in which non-destructive measurements on every unit are combined with reduced but continued reference testing, with the reference testing scaled back as evidence accumulates.

7.5 Data integrity, digital records and cybersecurity

Printed medicines generate electronic records at every step: design files, slicer settings, firmware versions, material lots, sensor outputs, alarms, analytical spectra and release decisions. These records should meet the ALCOA+ expectations of being attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available [25,26,85]. Audit trails, role-based access, time synchronisation, backup and tested recovery, and validation of computerised systems are required [86]. Because altering a design file changes the physical product, the integrity of the file repository is a patient-safety issue. Version control should prevent selection of obsolete or unapproved files, checksums or hashes should confirm that the file executed is the file approved, and network-connected printers should be protected against unauthorised modification. These controls become more demanding in decentralised settings, where many sites may print from a central library of designs [22].

8. Quality by design and quality risk management

QbD is a systematic approach that starts with predefined objectives and emphasises product and process understanding and control based on sound science and quality risk management [58,87,88]. It is well suited to printing, because the number of adjustable variables is large and their interactions are not intuitive. QbD is useful only when applied as a documented line of reasoning rather than as a set of labels.

8.1 Quality target product profile

The QTPP describes the intended product: dosage form, route, strength or strength range, release characteristics, stability, packaging and patient-related needs such as swallowability, palatability and age-appropriateness. Patient acceptability of printed shapes has been studied directly [21]. For a

printed product the QTPP should also state whether geometry is purely cosmetic or functional, and whether different strengths will be made by scaling dimensions, changing infill or changing formulation. Each choice has different implications for validation.

8.2 Risk assessment

Quality risk management identifies failure modes, their causes and effects, and the controls that prevent or detect them [89]. Failure mode and effects analysis (FMEA) and similar tools help to rank risks and decide where experimental work is needed. Risk scores support decisions; they do not replace evidence. A failure with severe consequences, such as printing from the wrong design file, may need a dependable control even if its estimated probability is low. Table 4 gives an illustrative set of failure modes for printed dosage forms. It is a template for adaptation, not a completed product-specific assessment.

Table 4. Illustrative failure modes for printed dosage forms and corresponding controls (template for product-specific risk assessment; no validated risk scores are implied).

Failure mode	Possible cause	CQAs affected	Prevention / detection	Decision to define in advance
Interrupted extrusion or deposition	Nozzle blockage, filament slip, powder bridging	Mass, dimensions, assay, uniformity	Pressure / feed telemetry, machine vision, unit mass, spectroscopy	Window of potentially affected units; hold and test criteria
Feedstock moisture drift	Storage, ambient humidity	Flow, extrusion stability, degradation	Moisture specification, controlled storage, trend review	Action limit; drying or rejection; re-test plan
Wrong or obsolete design file	Version-control failure, manual selection	Dose, geometry, release	Controlled repository, checksum verification, independent set-up check	Stop run; assess all potentially affected units
Drug sedimentation in paste	Long holding time, low viscosity	Content uniformity	Defined maximum hold time, re-mixing step, first/last unit testing	Maximum hold time; disposition of late units
Incomplete photocuring	Exposure variation, light attenuation by drug	Strength, residual monomer, stability	Cure validation, extractables testing, post-cure control	Whether reprocessing is permitted
Thermal degradation	Excess temperature or residence time	Assay, impurities	Thermal history study, temperature alarms, stability-indicating assay	Temperature limits and alarm response
Spectral model drift	Instrument ageing, new excipient lot, new geometry	False content prediction	Reference samples, control charts of residuals, out-of-domain flags	Suspend model-based release if criteria fail

8.3 Design of experiments and design space

DoE allows the effects and interactions of several factors, such as nozzle temperature, print speed, infill and feedstock moisture, to be estimated efficiently. Screening designs identify influential factors, and response-surface designs map their effects on CQAs. A design space is the multidimensional combination of material attributes and process parameters demonstrated to provide assurance of quality [58]. For printing it may include formulation composition, feedstock properties, geometric parameters and printer settings. A design space cannot be inferred from a handful of successful prints. It must be supported by adequate experimental coverage, an understanding of interactions and confirmation under realistic variability. Working within an approved design space gives regulatory flexibility; moving outside it requires assessment and, potentially, further validation.

This is the scientific basis for personalised dosing. If strengths within a qualified range are produced by scaling dimensions while keeping formulation and process constant, and if the effect of scaling on release and uniformity has been characterised, a new strength inside that range may not need fresh studies. Changes to polymer content, infill, layer height or release architecture are different in kind and may require new comparative dissolution, mechanical, stability or uniformity data.

8.4 Control strategy

The control strategy is the planned set of controls, derived from product and process understanding, that assures process performance and product quality [90]. For printing it typically combines material specifications and incoming tests; controlled design files and printer configurations; equipment qualification and calibration [91]; in-process monitoring and alarms; non-destructive measurements on each unit; reference testing on samples; and release criteria. For every element, the strategy should state the action limit, the escalation route, the handling of failed or missing measurements and the role of reference methods.

8.5 Lifecycle management

After initial validation, performance must be monitored and changes managed [90,92]. Trends in process data, deviations, complaints and analytical performance reveal drift. Changes to materials, printers, firmware, slicer software, design files and analytical models should pass through change control, which determines whether requalification, recalibration, a comparability study or revalidation is needed. Chemometric models need their own lifecycle: periodic checks against reference samples, monitoring of prediction residuals and out-of-domain rates, and defined triggers for model update.

8.6 Equipment qualification, cleaning and technology transfer

Printers used for medicines need the same qualification sequence as other manufacturing equipment: design, installation, operational and performance qualification [91]. For a printer, operational qualification should cover temperature accuracy at the nozzle and bed, positional accuracy of the axes, feed-rate calibration and the correct execution of approved files, and should be repeated after significant maintenance or firmware updates. Desktop printers designed for hobby or engineering use

were not built with cleanability, material compatibility or audit trails in mind, and adapting them for GMP use may need hardware and software changes.

Cleaning is often overlooked in printing studies. Nozzles, syringes, extruder screws, build plates and resin vats can retain drug, and a printer used for several products or strengths creates a risk of cross-contamination. Cleaning procedures should be validated with residue limits appropriate to the potency of the drugs involved, and dedicated or single-use parts should be considered where cleaning cannot be verified. In personalised workflows with frequent product changes, the time and cost of cleaning can determine whether the model is practical at all.

Transferring a process to another printer, even of the same model, requires a comparability exercise rather than simple copying of settings. Thermal profiles, sensor positions, nozzle wear and firmware behaviour can differ between units. The transfer protocol should identify the critical differences, compare material and process performance, and define acceptance criteria before routine use. The same applies with greater force to multi-site and point-of-care networks.

9. Validation of non-destructive methods

Validation should begin with a precise statement of intended use [31,32]. "NIR estimates drug content between 80% and 120% of label claim in printlets of formulation X printed on printer type Y, to support unit-level acceptance" is a very different claim from "NIR screens for gross formulation errors". The first is quantitative and supports release; the second is qualitative and supports a hold decision. Box 1 outlines the main elements of a validation protocol.

Box 1. Outline of a validation protocol for a non-destructive method applied to printed dosage forms

Intended use. Target CQA; formulations, strengths and geometries covered; qualitative or quantitative purpose; decision supported.

Reference method and traceability. Validated reference procedure; its precision; sample preparation; traceability of reference values to individual units.

Sample design. Representative strengths, geometries, batches, material lots, moisture and surface variation, and challenge samples; strict separation of calibration and independent test sets.

Measurement procedure. Instrument settings, sample presentation and orientation, environmental conditions, data-acquisition and preprocessing rules, system-suitability checks.

Performance characteristics. Specificity, accuracy, precision, range, robustness; for models, prediction error and bias on independent sets; for classifiers, false-acceptance and false-rejection rates; for imaging, resolution, repeatability and segmentation rules.

Acceptance criteria. Justified limits linked to the CQA specification, with allowance for prediction uncertainty.

Handling uncertain results. Out-of-domain detection; an "inconclusive" outcome that triggers reference testing; rules for instrument failure or missing data.
Lifecycle and change control. Periodic verification with reference samples; trending; triggers for recalibration or revalidation after changes to hardware, software, formulation or product range.

Three issues deserve emphasis. The first is sample design. Calibration and validation sets should include representative strengths, geometries, material lots, moisture levels and surface finishes, and should contain deliberately challenging samples, such as units printed at the edges of the operating range or with induced defects. If concentration varies only between batches, the model may learn batch rather than concentration.
The second is the treatment of uncertainty. Every non-destructive method will sometimes be wrong. A false acceptance releases a defective unit; a false rejection wastes a good one. These two error rates have very different consequences and should be estimated separately, ideally with independent challenge sets. For high-severity attributes such as dose, acceptance limits may need to be tightened to account for prediction error, and an "inconclusive" category, in which the unit is held for reference testing, is preferable to forcing a pass or fail.
The third is transfer and maintenance. A calibration developed on one spectrometer, printer or site will not necessarily perform on another. Standardisation approaches exist [74], but their success must be demonstrated rather than assumed. The method's performance after changes to hardware, software, formulation or the intended product range should be assessed before it continues to support decisions.
Validation also has to address the realities of small-batch production. Compendial sampling plans for uniformity of dosage units assume that units can be drawn from a reasonably large batch [61,62]. When a run contains a handful of units, the batch may need to be defined differently, for example as all units printed from one feedstock lot on one qualified printer within a defined period, and the sampling plan should reflect the process risks rather than a fixed number. Every-unit non-destructive measurement can strengthen the statistical basis of release in this situation, but only if the method's own uncertainty is known and accounted for. Reference testing of a smaller number of units then serves to confirm that the non-destructive predictions remain accurate.

10. Regulatory and compendial considerations

10.1 Applicable principles

No jurisdiction has yet issued a comprehensive drug-product guideline specific to pharmaceutical printing. This does not mean that printed medicines are unregulated. The general framework for pharmaceutical development, quality risk management, the pharmaceutical quality system, analytical validation and lifecycle management applies in full: ICH Q8(R2), Q9(R1), Q10, Q12, Q2(R2) and Q14 [31,32,58,89,90,92]. Good manufacturing practice, including expectations for computerised systems and for qualification and validation, applies to printing operations [86,91]. A review of this

area should distinguish binding legislation, non-binding guidance, compendial standards and scientific proposals, because these are often blurred in the secondary literature.

10.2 United States

The FDA reviews printed drug products through the normal application pathways, and the levetiracetam approval remains the principal precedent [1,8]. FDA staff have described the agency's research programme on printed drug products and the quality questions it raises [1]. The FDA guidance on technical considerations for additively manufactured medical devices [93] contains useful engineering concepts, including design control, software workflow, material controls and post-processing, but its scope is devices, and it should not be cited as a drug-product requirement. Guidance on PAT [83], NIR analytical procedures [69] and data integrity [25] is directly relevant to the analytical aspects discussed here.

10.3 European Union and United Kingdom

EMA guidelines on NIR spectroscopy [70] and real-time release testing [84], together with ICH guidelines, provide the main European reference points. The UK has gone furthest in creating a legal framework for decentralised production. The Human Medicines (Amendment) (Modular Manufacture and Point of Care) Regulations 2025, in force since 23 July 2025, introduce a regulatory route for medicines manufactured at or near the point of care and in modular units, and MHRA guidance lists printed products that can only be made at the point of care among the product types in scope [94]. This is the first framework to address directly the control of many manufacturing sites operating under a central quality system, and its implementation will be closely watched.

10.4 Pharmacopoeial requirements

The United States Pharmacopeia and the European Pharmacopoeia set requirements for uniformity of dosage units, dissolution and disintegration, and include general chapters on NIR, Raman and chemometrics [61,62,64,71,73,76]. A printed tablet is still a tablet. Unusual geometry may call for additional characterisation, but it does not remove compendial requirements. Where a non-destructive method is used in place of a compendial test, its equivalence or suitability must be justified in the application.

10.5 Unresolved questions

Several questions remain open. What constitutes a batch when each unit may be individually configured? How should sampling be designed for runs of a few units? Which design changes can be made within an approved design space, and which require a variation? Under what conditions can process and non-destructive data support release without destructive testing? How should responsibility be shared between a central license holder and a network of point-of-care sites? Early dialogue with regulators, through scientific advice or innovation offices, is advisable for any product that relies on novel release strategies.

11. A proposed integrated non-destructive verification framework

Drawing on the preceding sections, we propose a staged framework that places non-destructive verification within the wider quality system (Figure 2). Its central principle is that every measurement should have a stated intended use, a demonstrated link to a CQA and a predefined action when the result is unfavourable or uncertain.

Stage 1: Define. Establish the QTPP and CQAs, specify the approved design-file family and the qualified range of strengths and geometries, and identify which structural features are intentional.

Stage 2: Understand. Map CMAs and CPPs to CQAs through risk assessment, quantify the key relationships by DoE, and define the design space. Select conventional reference methods and generate a traceable reference data set that covers representative strengths, shapes, material lots and process conditions, including challenge samples.

Stage 3: Develop and validate. Screen candidate non-destructive methods against the CQAs they are meant to address. Build calibrations, test them on independent samples, estimate false-acceptance and false-rejection rates, and set model-domain limits.

Stage 4: Control during manufacture. Verify the design file and printer configuration before each run. Monitor feedstock and printer signals in real time, with alarms linked to segregation of affected units. Apply rapid non-destructive tests, such as machine vision for geometry and NIR or Raman for dose and identity, to every unit or to a defined high-frequency sample. Classify each unit as accepted, rejected or held for reference testing.

Stage 5: Verify and maintain. Continue periodic reference testing to confirm model performance, trend results, investigate deviations and manage changes. Revalidate when the formulation, printer, software, instrument or intended product range changes.

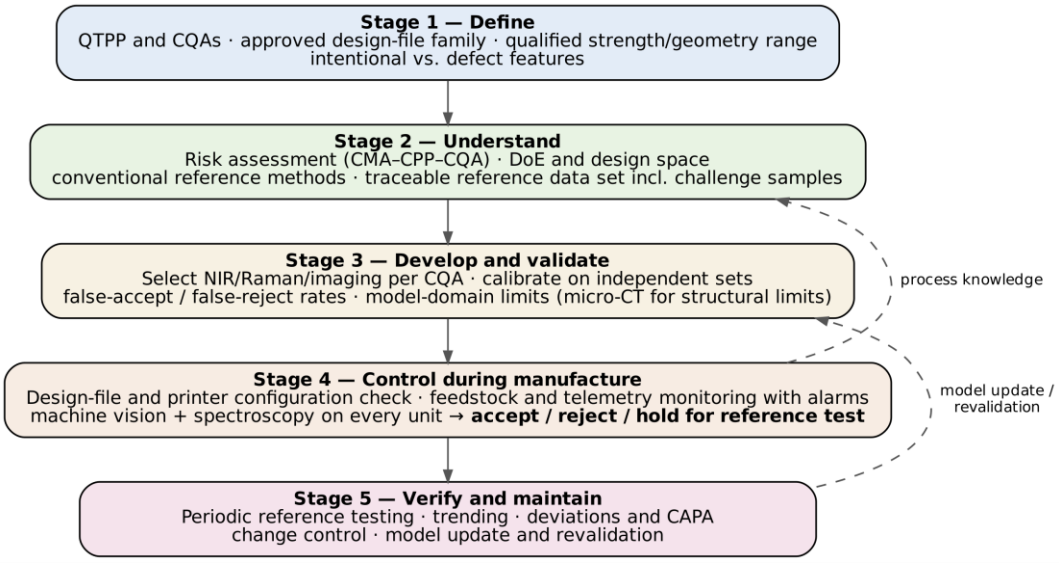


Figure 2. Proposed staged framework for integrated non-destructive quality verification of printed dosage forms. Solid arrows show the development sequence; dashed arrows show feedback during lifecycle management.

The framework is deliberately hybrid. It does not assume that non-destructive methods can replace reference testing from the outset. Instead, it allows the extent of destructive testing to be reduced in step with accumulated evidence. Micro-CT and other slower imaging methods sit mainly in Stages 2, 3 and 5, where they define structural limits and support investigations, rather than in routine unit-level release.

12. Research gaps and future directions

12.1 Reporting and comparability

The most immediate need is better reporting. Studies of non-destructive methods often omit the number of calibration and test units, the range of variation covered, the reference method's own precision, independent validation, prediction error with confidence intervals, and failure-detection performance. Without these data it is impossible to compare methods or judge readiness. Table 5 proposes a minimum reporting checklist.

Table 5. Proposed minimum reporting items for studies of non-destructive verification of printed dosage forms.

Item	What to report
Product and process	Platform and printer model; formulation; strengths and geometries; key process settings; number of batches and material lots
Intended use	Attribute measured; qualitative or quantitative purpose; decision the method is meant to support
Reference method	Method, its precision and accuracy, and how reference values were obtained for each unit
Sample design	Numbers of calibration and independent test units; range of concentration and other variables covered; inclusion of challenge or defective samples
Data processing	Instrument settings; spectral or image preprocessing; model type and selection; software and version
Performance	Bias, prediction error with confidence intervals, accuracy profile or equivalent; for classification, sensitivity, specificity, false-acceptance and false-rejection rates
Robustness and transfer	Effect of lot, instrument, operator, day, geometry and environmental changes; any transfer to other instruments or sites
Limits	Model domain and out-of-domain handling; known failure cases; unresolved limitations

12.2 Model transferability and robustness

Few studies test whether a calibration survives a change of printer, instrument, material lot or site, or holds up over months of use. Multi-site studies, deliberate perturbation experiments and long-term monitoring of deployed models would provide the evidence regulators will need.

12.3 Artificial intelligence

Machine learning has been applied to predicting printability and release, analysing images of printed units and optimising formulations [30,65,81]. These tools could improve defect recognition and reduce development time. They also raise concerns about opaque decisions, sensitivity to inputs outside the training distribution and silent model drift. Any AI model used to support a quality decision should be managed like any other analytical procedure, with a defined intended use, validation, version control, performance monitoring and change control.

12.4 Digital twins

A digital twin is a virtual representation of a process that is continuously updated with plant data and used to predict and control performance [95]. For printing, a twin that links design parameters, feedstock properties and printer telemetry to predicted CQAs could, in principle, support real-time release. Building one requires mechanistic understanding and data that do not yet exist for most printed products.

12.5 Decentralised and point-of-care manufacture

Printing in hospital pharmacies or other clinical settings has been demonstrated [13,22], and the UK framework now provides a legal route [94]. Quality assurance in this setting depends on standardised equipment and materials, centrally controlled design files, remote oversight of data, staff training and verification methods that can be operated by non-specialists. Non-destructive verification is arguably more important here than in centralised manufacture, because local laboratories may not be able to run full chromatographic testing.

12.6 Practical considerations

Implementation also depends on factors that rarely appear in technical papers: the total cost of quality, including analytical instruments, calibration sets and staff time; human factors in printer setup and data review; packaging that protects often fragile or hygroscopic printed units; labelling and identification of individually configured units; and occupational and environmental issues such as handling of potent powders, solvents and uncured resins. A lower material cost per unit does not necessarily mean a lower overall cost, and economic comparisons with conventional manufacture should be product-specific.

12.7 Limitations of this review

This is a narrative rather than a systematic review. Although searches were structured, study selection and synthesis involved judgement, and relevant work may have been missed. The evidence base is heterogeneous in platforms, formulations and methods, which limits direct comparison. Regulatory statements reflect documents available at the time of writing and should be checked against current versions.

13. CONCLUSIONS

Printing turns geometry into a formulation variable and dose into a software setting. These are its strengths, and they are also the reason why quality assurance for printed medicines cannot simply copy the approach used for compressed tablets. Destructive, sample-based testing becomes inefficient and sometimes impractical when batches are small and units differ.

Non-destructive methods can close much of this gap. Spectroscopy can verify identity, dose and solid state; imaging can confirm geometry and reveal internal defects; process monitoring can prevent many defects from occurring. Published studies show that these approaches work in principle. They also show that no single technique covers every attribute, and that most demonstrations remain at the proof-of-concept stage, with limited evidence on robustness, transferability and error rates.

The path forward is integration rather than replacement. A credible quality system for printed medicines combines controlled digital design, a well-understood CMA–CPP–CQA framework, complementary non-destructive measurements with stated intended uses, continued reference testing, and lifecycle management of both processes and models. Real-time release of printed medicines is achievable, but only when the evidence linking measured signals to patient-relevant quality attributes is as strong as the evidence that currently supports conventional release testing.

Declarations

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