State-of-the-Art Report: Regulatory Development of 3D-Printed Drug/Medicinal Products, Medical Devices, and Combination Products

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List of abbreviations

3D – Three-Dimensional

AI – Artificial Intelligence

ALCOA – Attributable, Legible, Contemporaneous, Original, Accurate (data integrity principles)

AM – Additive Manufacturing

ANDA – Abbreviated New Drug Application

ASTM – American Society for Testing and Materials

CBER – Center for Biologics Evaluation and Research (FDA)

CDER – Center for Drug Evaluation and Research (FDA)

CDRH – Center for Devices and Radiological Health (FDA)

CE – Conformité Européenne (European Conformity marking)

CFR – Code of Federal Regulations

DQ – Design Qualification

EC – European Commission

EMA – European Medicines Agency

EU – European Union

FAT – Factory Acceptance Testing

FDA – Food and Drug Administration (U.S.)

GMP – Good Manufacturing Practice

HAZOP – Hazard and Operability Study

HEPA – High-Efficiency Particulate Air (filter)

IQ – Installation Qualification

ISO – International Organization for Standardization

ITF – Innovation Task Force (EMA)

IVDR – In Vitro Diagnostic Regulation (EU)

MDR – Medical Devices Regulation (EU)

MEDDEV – Medical Devices Guidance Documents (EU)

NDA – New Drug Application

OQ – Operational Qualification

PAT – Process Analytical Technology

PMA – Premarket Approval (FDA)

PMOA – Principal Mode of Action

PQ – Performance Qualification

PRIME – PRIority MEdicines (EMA)

QMS – Quality Management Systems

RFD – Request for Designation (FDA)

SAT – Site Acceptance Testing

URS – User Requirements Specification

US – United States

1. Introduction

3D printing, also known as additive manufacturing (AM), is rapidly transforming the pharmaceutical and medical device industries by enabling the production of highly personalized medicines, complex medical devices, and innovative drug-device combination products. This technology enables rapid prototyping, customization, and on-demand manufacturing, making it especially valuable for personalized medicine, rare diseases, and complex anatomical applications. By enabling highly customized, patient-specific solutions previously unattainable with traditional manufacturing methods, 3D printing holds significant promise to improve patient outcomes, personalize treatments, and streamline supply chains in the healthcare sector.

However, the regulatory environment for 3D-printed medical products remains complex and is evolving to keep pace with technological advancements. Regulatory agencies worldwide are grappling with the challenge of ensuring product safety, quality, and efficacy while fostering innovation and addressing the unique risks associated with individualized manufacturing. This document aims to provide an overview of the current regulatory frameworks governing 3D-printed medicinal products and medical devices, highlight areas of ongoing development, and discuss the implications for manufacturers, healthcare providers, and patients. Through a comprehensive review of global and regional regulations, stakeholders can better understand the pathways to compliance and anticipate future trends in this dynamic field.

However, the regulatory frameworks in both the EU and the US are still adapting to the unique challenges and opportunities presented by these technologies. The regulatory landscape is characterized by a lack of harmonized, product-specific standards, evolving GMP requirements, and the need for multidisciplinary collaboration among manufacturers, regulators, and healthcare providers. (Härkönen, 2025; Reis et al., 2022) This report has been prepared as part of the **3D Printing for Personalized Medicine and Customized Drug Delivery (3D-CURE) project**, specifically within Work Package 3 – Anticipation of future regulation of 3D-printing of drug products and medical devices and its effects on research and product development. The insights presented aim to support strategic planning for regulatory compliance and innovation in the context of emerging 3D-printing technologies.

2. Current Regulatory Landscape

2.1 European Union (EU)

2.1.1. Medicinal Products

Regulatory Framework: There are currently no specific EU guidelines for 3D-printed medicinal products. In Finland, for example, patient-specific 3D printing is treated as ex tempore pharmacy production, with the pharmacist responsible for compliance within their license. These products do not have market approval and are not considered industrial manufacturing. (Fimea, 2024)

Regulatory agencies in the EU face ongoing challenges in keeping pace with the rapid advances in 3D printing technology. There is a growing emphasis on collaborative efforts between industry stakeholders and regulators to develop flexible guidance that addresses novel manufacturing processes, supply chain complexities, and patient-specific product risks. As regulatory adaptation continues, manufacturers are encouraged to engage early with competent authorities to clarify expectations and ensure compliance with evolving standards. (Härkönen, 2025; Fimea, 2024)

With the rapid adoption of 3D printing, regulators are confronted with new questions concerning product traceability, batch definition, and the validation of highly individualized processes. The absence of harmonized standards often results in case-by-case regulatory assessments, which can create uncertainty for manufacturers and healthcare providers. Moreover, the integration of digital design files, automation, and decentralized manufacturing models raises concerns about data security, intellectual property, and quality assurance throughout the product lifecycle. (Härkönen, 2025)

Industrial 3D Printing: Industrial-scale 3D printing of medicines is not yet legislated or integrated into licensed drug manufacturing in the EU. The European Medicines Agency (EMA) has recognized the need for regulatory adaptation, but has not yet issued comprehensive guidance. (Reis et al., 2022; Sipola, 2026)

GMP Requirements: All medicinal products must comply with EU GMP (EudraLex Volume 4), which covers the entire production process, including raw material sourcing, manufacturing, packaging, storage, and distribution. GMP requirements are broad and high-level, with detailed guidelines for sterile manufacturing, equipment qualification, and data integrity. (Härkönen, 2025; Sipola, 2026)

2.1.2. Medical Devices

Regulatory Framework: 3D-printed medical devices are regulated under the Medical Devices Regulation (MDR, EU 2017/745). Devices are classified by risk (Class I–III), with higher classes requiring more stringent controls, including clinical evaluation, post-market surveillance, and conformity assessment by notified bodies. (Härkönen, 2025; Fimea, 2024)

Examples of 3D-printed devices for each class include:

- Class I (Low Risk): 3D-printed anatomical models used for surgical planning, non-invasive surgical guides, and dental models. These devices generally do not come into direct contact with patients or are used for non-critical applications.
- Class II (Moderate Risk): 3D-printed surgical guides that are used in the operating room to direct instruments, dental crowns and bridges, external prosthetics such as limb sockets, and some orthopedic implants that do not support or sustain life.
- Class III (High Risk): 3D-printed implantable devices such as patient-specific cranial or maxillofacial implants, spinal cages, and heart valves. These devices are intended to be implanted in the body and are critical to sustaining or supporting life, or preventing impairment of health.

Custom-Made Devices: Custom-made 3D-printed devices are specifically designed to match the unique anatomy or clinical requirements of individual patients. Examples include patient-specific cranial plates tailored to reconstruct skull defects resulting from trauma or surgery, and custom mandibular implants used for jaw reconstruction in cases of congenital anomalies or after tumor removal. Additionally, custom-fit hearing aid shells and dental aligners are frequently produced using 3D printing to ensure optimal comfort and performance for each user.

Custom-made devices, including 3D-printed ones, have specific requirements under Annex XIII of the MDR. These include a technical file, a statement of conformity, and documentation of the device's intended use and design. Custom-made devices are exempt from some requirements, like CE marking and clinical evaluation reports, but must still ensure safety and performance. (Reis et al., 2022)

Technical Considerations: The MDR requires manufacturers to address technical aspects, including material selection, biocompatibility (ISO 10993), software validation, and risk management (ISO 14971). Cleanroom requirements (ISO 14644) and process validation are also critical.

In addition to these requirements, manufacturers must ensure robust traceability of both materials and production steps to facilitate post-market surveillance and potential product recalls. Documented procedures for the control and verification of digital design files are essential, particularly when devices are customized for individual patients. The use of automated manufacturing and decentralized production sites further underscores the need for strong data integrity measures, including cybersecurity protocols and secure data transfer methods.

Manufacturers are also expected to conduct thorough usability testing and human factors engineering to confirm that the final device meets performance specifications and is safe and effective for its intended use. Regular audits and ongoing monitoring of manufacturing environments help maintain compliance with ISO and MDR standards. Additionally, the MDR emphasizes the importance of continuous improvement, requiring manufacturers to update technical documentation and risk assessments as new information or technologies emerge. (Härkönen, 2025)

2.1.3. Combination Products

Regulatory Pathways: Drug-device combinations are regulated based on the principal mode of action (PMOA):

- If the medicinal action is primary, Directive 2001/83/EC applies, complemented by MDR requirements.
    - For example, a 3D-printed drug-eluting stent, which releases medication to prevent artery blockage while also providing structural support, is a type of drug-device combination regulated under these pathways. Another example includes transdermal patches with embedded micro-needles that deliver drugs directly through the skin, combining both device and medicinal product functionalities.
- Conversely, if the device action is primary, the MDR is the main regulatory framework, with medicinal product requirements as a complement.
    - An example of this is a 3D-printed orthopedic implant coated with an antibiotic layer: the implant's main purpose is to provide mechanical support or structural integration, while the antibiotic serves a secondary, supportive function to reduce infection risk. In this case, the device's therapeutic action is considered predominant, and the product is regulated as a medical device with additional oversight pertaining to the medicinal substance. (Reis et al., 2022)

Regulatory Challenges: Products with unclear or dual PMOA, such as 3D-printed scaffolds incorporating drugs whose function changes in response to external stimuli, pose significant regulatory challenges. The EU uses a complementary approach, but complex cases may require a merged regulatory strategy, as discussed in Reis et al. (2022), who propose a decision tree for classification and regulatory action.

The decision tree by Reis et al. is designed to help manufacturers and regulators determine the appropriate regulatory pathway for combination products, particularly those involving both drugs and devices. This decision tree considers the product's principal mode of action (PMOA)—whether the primary action is medicinal or device-related—and guides users through a series of questions and criteria to clarify whether the product falls under the main jurisdiction of medicinal product regulations, medical device regulations, or requires a combined approach. By systematically evaluating factors such as intended use, mechanism of action, and the integration of medicinal and device components, the decision-tree streamlines classification and helps ensure the correct application of relevant EU directives and MDR requirements.

Guidance Documents: The EMA's "Guideline on the quality documentation for medicinal products when used with a medical device" (2019) and MEDDEV 2.1/3 rev.3 provide non-binding guidance for manufacturers. The Helsinki Procedure (2021) allows for consultation among competent authorities on borderline and classification issues.

2.1.4. Good Manufacturing Practices (GMP)

In the European Union, the principles of Good Manufacturing Practice are defined in EudraLex Volume 4 and its accompanying annexes. These requirements set the framework for ensuring that medicinal products and combination products are manufactured consistently and in accordance with established quality standards. Central to GMP is the expectation that all critical processes are validated. The EU recognizes three acceptable approaches to process validation: the traditional model based on defined validation batches, continuous process verification, and a hybrid of the two. GMP obligations also extend to equipment qualification, cleanroom and environmental control, material traceability, and robust data-integrity practices, all of which form essential components of a compliant quality system (Härkönen, 2025; Sipola, 2026).

A structured qualification lifecycle governs the introduction and use of equipment in GMP environments. This lifecycle typically begins with the User Requirement Specification (URS), which defines the functional and performance needs for a given system. It is followed by

Design Qualification (DQ), Factory Acceptance Testing (FAT), and Site Acceptance Testing (SAT) to ensure that the equipment is fit for purpose and correctly installed. Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) then confirm that the equipment operates reliably, performs within predefined limits, and consistently supports compliant production (Härkönen, 2025).

2.1.5. Innovation Support

The EMA provides support for SMEs and academic researchers developing innovative products, including 3D-printed medicines and devices. The EU actively encourages innovation in the field of advanced therapeutics, including 3D-printed medicinal products and devices, through several mechanisms. These include the Innovation Task Force (ITF) at the European Medicines Agency (EMA), which provides early dialogue and scientific advice to developers of innovative products. Additionally, programs such as the PRIME (PRIority MEdicines) scheme offer enhanced support for medicines that target unmet medical needs, facilitating accelerated assessment and guidance throughout development. National agencies may also offer scientific advice and innovation offices to further support manufacturers navigating regulatory requirements for novel technologies. (Fimea, 2024)

2.2. United States (US)

2.2.1. Medicinal Products

Regulatory Framework: The FDA regulates 3D-printed drugs under existing pathways. As of now, the only 3D-printed drug approved by the FDA and released to the market is Spritam® (levetiracetam), approved in 2015 for the treatment of epilepsy. Spritam was developed using ZipDose® technology, allowing for rapid disintegration with a small amount of liquid. No other 3D-printed drugs have received FDA approval for market release to date, although several are in research and development stages. The FDA continues to evaluate applications and provide guidance on 3D-printed pharmaceuticals as the technology evolves. (Härkönen, 2025; Fimea, 2024)

Guidance Documents: The FDA has not yet issued specific guidance for 3D-printed drugs but applies existing regulations for drug approval, including New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) pathways (Sipola, 2026).

2.2.2. Medical Devices

Regulatory Framework: The FDA's Center for Devices and Radiological Health (CDRH) regulates 3D-printed medical devices. Devices are classified by risk (Class I–III), with regulatory controls increasing with risk. For example, 3D-printed surgical instruments such as forceps or anatomical models used for pre-surgical planning are typically Class I (low risk). Dental crowns, hearing aids, and orthopedic implants like cranial plates or bone screws produced by 3D printing are often classified as Class II (moderate risk). High-risk, life-supporting or life-sustaining devices such as 3D-printed heart valves or spinal interbody fusion devices are generally considered Class III and require the most rigorous premarket review and controls.

Devices cleared or approved through the FDA's regulatory pathways must demonstrate safety and effectiveness based on their intended use and risk classification. The premarket submission process may require clinical data, bench testing, and comprehensive documentation of the manufacturing process, especially for Class III devices. The FDA also encourages early interaction through its Q-Submission program, which allows manufacturers to seek feedback on regulatory strategies and technical challenges during product development. (U.S. Food and Drug Administration, 2017)

Guidance Documents: The FDA's "Technical Considerations for Additive Manufactured Medical Devices" document provides comprehensive guidance on the unique aspects of 3D-printed (additively manufactured) medical devices. It addresses specific topics, including device design, material controls, manufacturing process validation, and post-processing steps. The guidance emphasizes the importance of documenting each stage of production, including software workflows and quality assurance measures, to ensure consistency, safety, and effectiveness of 3D-printed devices. Additionally, the document outlines recommended testing methods and reporting requirements for manufacturers submitting devices for FDA review, helping them navigate the regulatory expectations for innovative manufacturing technologies. (U.S. Food and Drug Administration, 2017)

2.2.3. Combination Products

Regulatory Pathways: In the United States, oversight of combination products is coordinated by the FDA's Office of Combination Products (OCP), which determines the primary regulatory pathway based on the product's principal mode of action (PMOA). Depending on whether the dominant effect is pharmacological, device-related, or biological, the review is led by CDER, CDRH, or CBER, respectively. Although a single center assumes primary responsibility, the FDA applies an integrated, cross-center approach to ensure comprehensive evaluation of all

constituent parts. Compared to the EU, the US framework has developed more rapidly in issuing targeted guidance specific to combination products and, increasingly, to additive manufacturing. (Reis et al., 2022; Sipola, 2026)

Guidance Documents: The FDA applies current Good Manufacturing Practice (cGMP) requirements according to the nature of each constituent part: 21 CFR Parts 210 and 211 for drug components, Part 820 for device components, and Part 4 for combination products. Part 4 clarifies how overlapping requirements should be interpreted and implemented within a single quality system, emphasizing risk-based decision-making and lifecycle control. Process validation is expected throughout the manufacturing lifecycle, supported by robust documentation, data integrity measures, and traceability of materials and process decisions. The FDA has also issued a growing body of guidance documents addressing combination products, software assurance, digital systems, and emerging production technologies, which collectively support a more integrated and responsive regulatory environment for combination product development. (Sipola, 2026)

2.2.4. Good Manufacturing Practices (GMP)

In the United States, current Good Manufacturing Practice (cGMP) requirements form the foundation for ensuring that medicinal products, medical devices, and combination products are manufactured consistently and in accordance with established quality standards. The FDA's cGMP framework encompasses every aspect of production, including equipment qualification, process validation, material and component control, and overall quality assurance. These requirements are designed to ensure that manufacturing processes remain in a state of control throughout the product lifecycle.

To support industry implementation, the FDA has issued a series of guidance documents addressing key elements of cGMP compliance. This includes detailed expectations for data integrity, reflecting the agency's emphasis on reliable, attributable, and traceable records, as well as guidance on process validation principles that outline the lifecycle approach to establishing and maintaining process robustness. In addition, the FDA has published technical guidance on additive manufacturing of medical devices, which provides considerations relevant to emerging production technologies and increasingly applies to combination products utilizing 3D-printing. (Sipola, 2026; U.S. Food and Drug Administration, 2017)

3. Key Regulatory Challenges

3.1. Classification and PMOA

Determining the Principal Mode of Action (PMOA) is central to selecting the appropriate regulatory pathway for combination products. For advanced or multifunctional products—such as 3D-printed scaffolds that provide structural support while releasing a medicinal substance in response to external stimuli—the PMOA may not be immediately evident. In such cases, the classification cannot rely on a straightforward interpretation of the primary therapeutic effect. Instead, a case-by-case assessment is often necessary, and in some instances a blended or coordinated regulatory approach may be required to ensure that all relevant safety, quality, and performance considerations are addressed (Reis et al., 2022).

To support more consistent decision-making in these complex scenarios, Reis et al. (2022) propose a structured decision-tree model for combination product classification. The model considers factors such as the nature and function of the medicinal substance, the intended therapeutic action, the urgency and risk profile of the clinical application, characteristics of the manufacturing process, and the presence of design features or trigger mechanisms that influence product behaviour. This type of systematic tool can help manufacturers and regulators reach clearer, more predictable conclusions about product classification, particularly as emerging technologies blur the traditional boundaries between medicinal products and medical devices. (Reis et al., 2022).

3.2. Lack of Harmonized Standards

A persistent challenge in the regulation of 3D-printed medicinal products and combination products is the absence of harmonized, product-specific standards across major regulatory regions. In the European Union, dedicated standards for additively manufactured medicinal products remain limited, creating variability in interpretation and expectations. Although the United States has issued more targeted guidance—particularly for medical devices and emerging manufacturing technologies—both regions continue to face difficulties keeping regulatory frameworks aligned with the pace of technological development. (Sipola, 2026; Härkönen, 2025)

At the international level, standardization efforts are progressing but remain incomplete. ISO/ASTM 52900 provides foundational terminology and general principles for additive manufacturing, establishing a common language for processes and materials. However, detailed product-specific standards tailored to pharmaceutical applications are still under

development. As additive manufacturing becomes more widely integrated into drug and combination-product manufacturing, the need for consistent, globally recognized technical and quality standards will become increasingly important.

3.3. Manufacturing and Quality Assurance

Process validation plays a central role in the manufacturing of 3D-printed medicinal and combination products, as additive manufacturing introduces a set of risks that differ from those encountered in conventional production. Variability in digital design, material properties, layer-by-layer construction, and post-processing can all influence the critical quality attributes of the finished product. Both the EU and US regulatory frameworks require that manufacturers identify and validate the critical process parameters that affect product quality and safety. Although the core principles are similar across regions, the United States has provided more detailed guidance for additive manufacturing—particularly for medical devices—offering clearer expectations for process documentation, verification, and risk mitigation. (U.S. Food and Drug Administration, 2017; Sipola, 2026)

The design of 3D-printing equipment used in pharmaceutical and combination product manufacturing is equally important for ensuring regulatory compliance and reliable quality. Equipment must be constructed from materials compatible with the substances being processed and designed to support effective cleaning, maintenance, and contamination control. Closed systems, HEPA-filtered environments, and automated monitoring of temperature, humidity, and particulates can significantly reduce variation and help maintain consistent print quality. Robust control systems that manage key operational parameters—such as print resolution, energy input, and environmental conditions—are essential for ensuring that the printed output remains within predefined specifications.

Integration with digital quality management systems further enhances process oversight by enabling real-time monitoring and documentation of equipment performance. This is particularly relevant for additive manufacturing, where traceability from digital design to finished product is critical. To maintain accuracy, reliability, and compliance with cGMP expectations, equipment must undergo regular qualification and calibration. The qualification lifecycle includes clearly defining user needs through a User Requirement Specification (URS), assessing design suitability during Design Qualification (DQ), and verifying proper performance through Factory Acceptance Testing (FAT), Site Acceptance Testing (SAT), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). Collectively, these elements ensure that the equipment consistently operates within controlled limits and supports the production of safe, high-quality products.

(Härkönen, 2025)

3.4. Data Integrity and Traceability

Ensuring data integrity and maintaining full traceability are critical regulatory expectations in both the EU and the US, particularly for 3D-printed and personalized products where batch sizes may be small and product characteristics inherently variable. Regulators place strong emphasis on the reliability and authenticity of all manufacturing and quality-related data, as these elements form the foundation for demonstrating product safety, quality, and performance throughout the lifecycle.

The principles commonly referred to as **ALCOA**—Attributable, Legible, Contemporaneous, Original, and Accurate—provide the core framework for data integrity within regulated industries, including pharmaceutical manufacturing and emerging additive-manufacturing applications. These principles require that every data entry can be traced to a specific individual or system; that documentation is clear and comprehensible; that information is recorded at the time the activity occurs; that the record represents the original data or a certified true copy; and that all entries accurately reflect the event or measurement. Adherence to ALCOA is fundamental to maintaining trustworthy records and is reinforced across both EU GMP and FDA cGMP expectations. (Härkönen, 2025; Sipola, 2026)

In the context of 3D-printed medicinal and combination products, the reliance on digital workflows adds an additional layer of regulatory scrutiny. Electronic systems used for modeling, segmentation, printer control, batch documentation, and quality testing must be validated to ensure that electronic records comply with ALCOA principles and remain tamper-evident, traceable, and audit-ready. This requirement extends to software audit trails, system access controls, version management, and the long-term preservation of digital design files and manufacturing data.

Batch management also becomes more complex for personalized or small-batch products. Traditional definitions of a batch—as a homogeneous quantity produced under uniform conditions—may not fully apply when each unit is produced individually or modified based on patient-specific data. To support regulatory expectations, manufacturers are encouraged to implement digital recordkeeping systems that enable precise tracking of each unit, including automated batch numbering, electronic documentation of critical process parameters, and seamless integration with the overarching quality management system. These measures help ensure that every product can be traced back to its material sources,

digital design inputs, manufacturing parameters, and quality control outcomes, enabling regulators and manufacturers to maintain high standards of oversight. (Härkönen, 2025)

4. Guidance for Research and Product Development

4.1. Early Regulatory Engagement

Early and proactive interaction with regulatory authorities is a critical component of the development pathway for novel or complex drug–device combination products. Engaging with agencies such as the EMA and FDA at an early stage helps clarify regulatory expectations, identify potential challenges, and guide the selection of appropriate development and validation strategies. Innovation support mechanisms—such as scientific advice procedures, innovation offices, and early consultation programs—offer valuable opportunities to discuss product concepts, manufacturing approaches, and clinical considerations before formal submissions are made. (Fimea, 2024)

Effective early engagement is strengthened by close collaboration among the various stakeholders involved in product development. Multidisciplinary cooperation between manufacturers, regulatory authorities, healthcare professionals, and technical experts enables a more comprehensive understanding of both regulatory and clinical requirements. This collaborative approach is particularly important for emerging technologies like additive manufacturing, where shared expertise contributes to better risk identification, more robust development plans, and ultimately, improved patient safety. (Reis et al., 2022)

4.2. Risk Management and Process Validation

Effective risk management is essential throughout the entire lifecycle of 3D-printed drug–device combination products. Comprehensive risk assessments—such as HAZOP analyses—should be conducted for each stage of the manufacturing process, beginning with imaging and digital design and extending through material preparation, printing, post-processing, and final packaging. These assessments help identify potential sources of variability or failure, clarify the interactions between process steps, and support the development of appropriate control strategies. (Sipola, 2026)

Process validation plays a central role in ensuring that the manufacturing system consistently produces products that meet predefined quality attributes. All critical process parameters and quality attributes must be defined, justified, and validated, with full documentation of the methods used, the rationale for acceptance criteria, and any deviations

encountered. Corrective and preventive actions should be recorded and assessed to maintain control. As additive manufacturing technologies evolve, the use of advanced tools such as Process Analytical Technology (PAT) and continuous process verification can further strengthen process understanding by enabling real-time monitoring and more dynamic control of production conditions. These approaches support both regulatory compliance and product reliability, particularly in manufacturing processes where personalized product variations introduce additional complexity. (Sipola, 2026)

4.3. Quality Management Systems (QMS)

A robust, well-structured Quality Management System is essential to ensuring consistent control over the development and manufacturing of drug–device combination products produced using advanced or additive manufacturing technologies. In the EU, QMS requirements are defined primarily through ISO 13485:2016, while in the United States, comparable expectations are outlined in 21 CFR Part 820. Together, these frameworks establish the foundation for document control, change management, training, handling nonconformities, and other elements necessary to maintain continuous quality assurance. Compliance with these standards also supports the generation and maintenance of detailed, traceable quality records, including those related to material selection, manufacturing activities, and product testing. For combination products that incorporate medicinal substances or are intended for clinical use, biocompatibility testing—such as that outlined in ISO 10993—remains an essential part of demonstrating product safety. (Härkönen, 2025; U.S. Food and Drug Administration, 2017)

Implementing a compliant QMS also requires systematically qualifying all equipment used in the manufacturing process. This includes defining user needs through a User Requirement Specification (URS), assessing the suitability of the design during Design Qualification (DQ), and confirming proper installation and operation through Factory Acceptance Testing (FAT), Site Acceptance Testing (SAT), Installation Qualification (IQ), and Operational Qualification (OQ). Performance Qualification (PQ) then verifies that the equipment consistently operates within predetermined parameters under routine production conditions. Following this structured lifecycle ensures that equipment is reliable, traceable, and fully aligned with GMP and cGMP expectations, enabling reproducible and high-quality manufacturing outcomes. (Härkönen, 2025)

4.4. Material and Software Controls

Effective control of both materials and software is essential for ensuring the quality, safety, and regulatory compliance of 3D-printed drug–device combination products. All materials used in manufacturing must be fully documented, including detailed information on suppliers, specifications, and certificates of analysis. This documentation supports traceability and provides an auditable basis for verifying material quality throughout the lifecycle. In addition, careful assessment of material compatibility and biocompatibility is required to ensure that the selected substances perform reliably within the intended design and do not introduce risks to patient safety. (Härkönen, 2025)

Given the central role of digital workflows in additive manufacturing, software validation is equally critical. Software used for imaging, segmentation, design, slicing, printer control, and quality evaluation must operate within validated parameters to ensure consistent and reproducible outcomes. Regulatory expectations focus on ensuring that electronic systems maintain data integrity, enforce access controls, and generate complete and tamper-evident audit trails. Proper software lifecycle management—in alignment with FDA and EU requirements—is essential for maintaining reliable electronic records and supporting traceability across all stages of design and manufacturing. (Härkönen, 2025; U.S. Food and Drug Administration, 2017)

4.5. Batch and Traceability Management

Effective batch definition and traceability are particularly important for personalized and small-batch 3D-printed products, where unit-to-unit variability may be inherent to the manufacturing approach. Clear strategies are needed to ensure that every product can be fully traced from raw material source through digital design, production, quality control, and ultimately to the patient. This level of traceability is essential for demonstrating compliance with regulatory expectations and maintaining control over individualized manufacturing workflows. (Härkönen, 2025; Sipola, 2026)

Digital systems play a central role in enabling this level of oversight. The use of electronic records, automated batch numbering, and seamless integration with the organization's quality management system strengthens documentation accuracy and supports lifecycle traceability. These tools also help ensure that all relevant process data—such as material lot numbers, critical process parameters, equipment settings, and inspection results—are captured consistently and stored in a manner that meets regulatory requirements for completeness, data integrity, and audit readiness.

4.6. Stay Informed on Regulatory Developments

Continuous awareness of regulatory developments is essential for organizations working with 3D-printed medicinal products, medical devices, and combination products. Both the EU and the US frequently update their regulatory frameworks to reflect advances in additive manufacturing, digital health technologies, and integrated product design. Monitoring new guidance documents, consultation drafts, and regulatory communications helps ensure that development activities remain aligned with evolving expectations and emerging compliance requirements. Active participation in public consultations, regulatory workshops, and industry forums further supports early identification of upcoming changes and facilitates timely adaptation to new regulatory landscapes. (Sipola, 2026)

Standardization efforts play a similarly important role in shaping the future regulatory environment. Engagement with international standardization bodies such as ISO and ASTM enables manufacturers and researchers to contribute to the development of product-specific standards and technical specifications for 3D-printed products. Involvement in these initiatives not only helps shape practical, scientifically grounded standards but also enables organizations to align their processes with emerging global expectations, supporting both regulatory compliance and broader market access.

5. Regulatory Decision-Tree

Step 1: Is the product a combination of drug and device?

- If NO: Follow standard device or drug pathway.
- If YES: Continue.

Step 2: What is the Principal Mode of Action (PMOA)?

- Pharmacological, immunological, or metabolic (drug-led):
    - EU: Directive 2001/83/EC + MDR Annex I
    - US: Drug pathway (NDA/ANDA), cGMP, device requirements as applicable.
- Physical (device-led):
    - EU: MDR 2017/745 + consultation on medicinal component
    - US: Device pathway (510(k), PMA), cGMP, drug requirements as applicable.

Step 3: Is the product custom-made or patient-specific?

- If YES:
    - EU: MDR Annex XIII (custom-made device), technical file, statement of conformity, and some exemptions.
    - US: Custom device exemption (limited to 5 units/year), otherwise standard pathway.

Step 4: Does the product have an unclear or dual PMOA (e.g., function changes with external stimulus)?

- If YES:
    - EU: Case-by-case assessment, possible merged regulatory approach (consult EMA/Competent Authority).
    - US: Request for Designation (RFD) to the FDA Office of Combination Products.

Step 5: Are there novel materials, software, or manufacturing methods?

- If YES:
    - Engage early with regulators (EMA, FDA).

- Prepare for additional data on safety, biocompatibility, and process validation.

Step 6: Is the product intended for industrial or ex tempore (pharmacy) production?

- If ex tempore:
  - EU: Pharmacy compounding rules, pharmacist responsibility.
- If industrial:
  - Full GMP, QMS, and regulatory submission required.

6. Checklist for Research and Development Teams

A. Early Development

- ✓ Define intended use, patient population, and personalization needs (Härkönen, 2025).
- ✓ Identify if the product is a drug, device, or combination (Reis et al., 2022).
- ✓ Determine PMOA and regulatory pathway (Sipola, 2026).
- ✓ Engage with regulatory authorities (EMA, FDA) for scientific advice (Fimea, 2024).

B. Design and Manufacturing

- ✓ Select appropriate 3D printing technology and materials; ensure biocompatibility (Härkönen, 2025).
- ✓ Develop User Requirement Specification (URS) and Design Qualification (DQ) (Härkönen, 2025)
- ✓ Validate software and digital workflows for design and manufacturing (U.S. Food and Drug Administration, 2017).
- ✓ Establish process controls and document all parameters (U.S. Food and Drug Administration, 2017).
- ✓ Plan for a cleanroom and GMP-compliant production environment (Härkönen, 2025).

C. Quality and Risk Management

- ✓ Conduct risk assessments (e.g., HAZOP) for all process stages (Sipola, 2026).
- ✓ Validate all critical process parameters and quality attributes (Sipola, 2026).
- ✓ Implement robust QMS (ISO 13485:2016, 21 CFR 820) (Härkönen, 2025).
- ✓ Ensure traceability and data integrity throughout the product lifecycle (Härkönen, 2025).

D. Regulatory Submission

- ✓ Prepare technical documentation (device file, drug dossier, combination file as needed) (Reis et al., 2022).

- ✓ Include evidence of process validation, biocompatibility, and clinical evaluation (U.S. Food and Drug Administration, 2017).
- ✓ For combination products, provide rationale for PMOA and regulatory pathway (Reis et al., 2022).
- ✓ Address any novel aspects (materials, software, manufacturing) with additional data and justification (Sipola, 2026).

E. Post-Market and Continuous Improvement

- ✓ Monitor product performance and collect post-market data (Härkönen, 2025).
- ✓ Update risk assessments and process validation as needed (Sipola, 2026).
- ✓ Stay informed on regulatory updates and participate in industry consultations (Härkönen, 2025).

7. Future Outlook

The regulatory landscape for 3D-printed medicinal products, medical devices, and drug–device combination products is evolving rapidly as technological capabilities advance and the role of personalization in therapy expands. As noted by Härkönen (2025) and Sipola (2026), both the EU and the US are actively reshaping their regulatory frameworks, although at different speeds and through different mechanisms. In the EU, broad pharmaceutical legislative reforms aim to improve regulatory clarity, strengthen harmonization across Member States, and ensure that emerging technologies can be incorporated without compromising patient safety. The United States, supported by the Office of Combination Products, continues to publish targeted guidance on advanced manufacturing, combination products, digital systems, and additive manufacturing, enabling faster adaptation to new technological trends.

Standardization will remain central to the future direction of regulation. International initiatives—particularly those led by ISO and ASTM—are gradually developing product- and process-specific standards for additive manufacturing. These efforts are expected to reduce regional variability and offer clearer expectations for materials, process controls, and product-testing methodologies. As Härkönen (2025) highlights, increased harmonization will be crucial for global market access and for enabling cross-border consistency in regulatory oversight.

Digitalization is increasingly integral to the design and production process. High-resolution imaging, automated segmentation, machine-learning-supported design, and real-time process monitoring offer substantial improvements in precision but also introduce new regulatory considerations. Ensuring data integrity, validating software systems, and maintaining cybersecurity will become more complex as digital workflows grow in scale and interconnectivity. These developments echo the challenges described earlier in regulatory discussions, where expanded oversight of software quality and artificial intelligence will be necessary to maintain trust and transparency in automated or semi-automated decision-making (Härkönen, 2025).

Personalized medicine is expected to be one of the main beneficiaries of additive manufacturing. As described by Reis et al. (2022) and supported by Sipola (2026), 3D printing enables tailored geometries, individualized dosage forms, and patient-specific implants that address anatomical and physiological variation in ways traditional manufacturing cannot. However, these benefits also bring new regulatory dilemmas. Personalized products do not always conform to conventional GMP assumptions, particularly regarding batch definition, validation strategies, and acceptance criteria. When each product may differ in geometry, material behavior, or drug loading, regulators must determine how product-specific specifications can be justified, validated, and certified within a consistent quality framework.

Material quality will remain foundational to the regulatory trajectory. Luo et al. (2025) emphasize that clinical-grade biomaterials significantly reduce the risks associated with non-clinical materials, such as endotoxin contamination or unstable mechanical performance. They also align more naturally with GMP expectations for traceability and safety. At the same time, the printability and stability of materials must be carefully controlled. Even minor variations in component ratios or viscosity may affect structural integrity or drug-release characteristics, reinforcing the need for robust supplier oversight and method validation.

Process Analytical Technology (PAT) offers an important opportunity to improve consistency in 3D-printed medicinal products. While PAT frameworks have been widely adopted elsewhere in pharmaceutical manufacturing, their application to additive manufacturing remains limited. Studies of 3D-printed combination products have shown that simultaneous and interacting deviations—such as those occurring during extrusion, curing, or crosslinking—are difficult to fully capture using traditional HAZOP-based risk assessments. Future regulatory frameworks are likely to encourage broader adoption of PAT and

continuous process verification strategies to ensure the stability of individualized production processes.

Despite differences between EU and US regulatory approaches, both regions continue to emphasize traceability, documentation, and data integrity, suggesting substantial common ground for future convergence. As Härkönen (2025) notes, collaboration among equipment manufacturers, pharmaceutical developers, and regulatory authorities will be essential to ensuring that evolving manufacturing techniques are adopted safely and efficiently.

Looking forward, regulatory frameworks will need to incorporate more detailed guidance on additive manufacturing, digital system validation, and combination-product oversight. The ongoing modernization of EU legislation and the steady release of FDA guidance documents offer opportunities to address long-standing gaps related to material qualification, imaging workflows, PAT integration, and quality assurance for individualized or decentralized production models. Future work will also need to consider MDR-related interactions, cybersecurity requirements, and the role of hospital- or pharmacy-based manufacturing environments. Maintaining a balance between innovation and rigorous regulatory control will be key to enabling the safe and scalable implementation of 3D-printed drug–device combination products in clinical practice.

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