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Inspections and Pharmaceutical Quality Offices

Questions & Answers on the Implementation of 3DP Technology (Additive Manufacturing Technology) for Solid Oral Dosage Forms

1. Introduction

Three-dimensional printing (3DP) is an emerging technology with great potential in pharmaceutical applications, providing an innovative manufacturing solution for patient centred dosage forms.

3DP is an umbrella term, including a variety of different printing technologies that permit the manufacturing of solid structures by depositing successive layers of materials. Dosage forms are produced from a digital 3D file, such as a computer-aided design (CAD) drawing.

The 3DP technology can benefit finished product design by facilitating patient-centric treatment and by developing personalised medicines with e.g. a wide spectrum of dosage levels, shapes, flavours, colours, or drug combinations, all tailored to the specific needs of each patient or disease condition. These characteristics make this technology particularly advantageous for diverse patient groups, including paediatrics, geriatrics, those on multiple medications, and individuals with rare diseases.

Moreover, 3DP can integrate rapid manufacturing, with compact equipment, fewer production steps, automated and digital production processes, and a faster changeover, e.g. for small-scale solid dosage forms production.

2. Scope of the Questions and Answers

The aim of this document is to provide guidance on Quality and Good Manufacturing Practice (GMP) requirements to support the use of 3DP technology in pharmaceutical manufacturing of solid oral dosage forms. This document focuses on some specific Quality and GMP requirements but should be read in conjunction with all other relevant EU guidelines.

This document is applicable to both human and veterinary medicinal products covered by a marketing authorisation according to Directive 2001/83/EC or Regulation (EU) 2019/6.

The principles here described may also be relevant in the context of investigational medicinal products for Clinical Trial Applications (according to Regulation (EU) No. 536/2014, article 9 of the Regulation (EU) 2019/6, and EMA/CHMP/QWP/545525/2017 Rev. 2), and applicants are advised to liaise with the relevant National Competent Authorities (NCAs) responsible for the approval and supervision of their clinical trials.

Pharmacy preparations according to Directive 2001/83/EC, article 3, are regulated according to National legislation requirements, in which applicants are advised to liaise with the relevant NCAs.

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This document may evolve in the future, as the use of this technology evolves and more pharmaceutical applications are seen.

3. What quality requirements are relevant and applicable to support the use of 3DP in pharmaceutical manufacturing?

Pharmaceutical Development

The choice of a 3DP technology may depend on the active substance properties (e.g. solubility, melting point, degradation temperature, biopharmaceutical classification system (BCS) class, etc.), the selection of feed material(s), and the intended scale of production.

The properties of the active substance(s) and the excipient(s), and the manufacturing operations that are critical to product quality and safety and relevant to product performance and manufacturability, should be defined during pharmaceutical development.

Depending on the technology and the printer used, properties that may impact product and process performance are for instance:

- Rheological properties and extrudability/printability profile of the formulation to be printed.
- Physical state (crystalline or amorphous) of the active substance within the printed dosage form (and its related impact on dissolution/PK behaviour).
- Particle size of the raw materials.
- Compatibility of the active substance(s) with excipient(s).
- Stability of the active substance(s)/excipient(s) (including, e.g. stability towards printing temperature).

The impact of the 3DP technology and the manufacturing process on the properties of the finished product should be evaluated. The characteristics and/or critical quality attributes (CQAs) of the printed dosage form which should be considered and investigated include, but are not limited to:

- Appearance e.g. appropriate size, colour and shape for the specific patient group(s) or animal species.
- Uniformity of mass/content.
- Disintegration.
- Dissolution (and its influence on bioavailability and, if applicable, on bioequivalence).
- Porosity (and its related impact on mechanical strength, disintegration and dissolution).
- Assay and degradation products.
- Stability of the finished product (including considerations to, e.g. different strengths, batch sizes as relevant).

Some 3DP processes include the use of cartridge, or syringe, containing the formulation to be printed. The cartridge/syringe formulation may include active substance(s), excipient(s), or mixtures of ingredients. These intermediate products are often referred to as pharma inks. Several materials can be used in 3DP manufacturing, e.g. polymers, that can be used for their melting, solidification and binding properties under controlled conditions or solvents. These materials serve as carriers for active substances, which are highly adaptable to create complex and customised drug delivery systems, while ensuring uniform dispersion and, in some cases, controlled release.

Cartridges/syringes are critical components. Cartridges/syringes can be single-use or multi-use.

The stability of the formulation within the cartridge/syringe should be studied. It should be assured that the storage of the cartridge and number of re-uses, if applicable, have no impact on the stability of the finished product during shelf-life. In case of multiple uses, the physical-chemical and microbiological stability, before and after opening, should be investigated by:

- In-use studies reflecting the intended use of the cartridge (e.g. number of re-uses, storage conditions).
- Thermal cycling studies to ensure that the formulation can withstand temperature changes sustained by the cartridge each time it is heated for printing, if applicable.
- Appropriate rheological studies and texture analysis to evaluate the rheological behaviour and extrudability profile upon multiple uses.

In case of a suspension or a dry mixture, which may be prone to segregation during storage and transportation, the homogeneity of the formulation should be evaluated during development and confirmed by process validation and stability studies to ensure the correct dose delivery during printing. These studies should include assessment of multiple uses of the cartridges/syringes, if applicable.

The selection, optimisation and control of the 3DP process are also important aspects of the pharmaceutical development. The active substance(s) can be subject to different stresses depending on the technique used. This, in turn, can have an impact on the impurity profile of the product according to the active substance structure and properties. Therefore, during development it is important to consider the critical formulation attributes (e.g. stability of the formulation, solubilised or dispersed active substance in the formulation) together with the available manufacturing process options, in order to justify the selection of the 3DP process and confirm its appropriateness.

When developing a 3DP manufacturing process and its control strategy, it is important to consider the characteristics of the equipment that can affect process performance.

The manufacturing process development should consider equipment design and configuration, and identify the critical process parameters (CPPs) that should be monitored or controlled to ensure that the finished product is of the desired quality, e.g. depending on the technology used, the CPPs influencing the accuracy of the deposition may include, but are not limited to:

- Design of the nozzle (e.g. diameter, shape).
- Temperature (e.g. printing head, printing bed and chamber temperature).
- Pressure of extrusion.
- Speed of printing.
- Jetting frequency (for drop on demand inkjet printing).

Quality by Design (QbD) principles are well-suited for 3DP. These principles could be implemented in the development of formulations through thorough characterisation of the pharma ink, and in the development of the printing process through establishment of a design space. A good understanding of the properties of the raw materials, CPPs, finished product CQAs and their inter-relationships, is the starting point of manufacturing process qualification (see for further reference the ICH guideline Q8 (R2), and the EMA Questions and answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters).

Process Validation

The process validation should be performed in accordance with the EMA Guideline on process validation for finished products (see references below). As a process involving new technologies, 3DP should be considered as a non-standard manufacturing process, in line with Annex II of that guideline. The process validation should be conducted with the printer which is intended to be used for routine commercial production. When technical changes are made to the equipment, the relevance of previous validation studies should be evaluated, and the level of re-validation studies required should be determined by appropriate risk analysis. In case the validation is carried out at the level of the ink manufacturer/printer supplier and the technology is transferred to the end user, the end user should demonstrate the robustness and reproducibility of the process by manufacturing a justified number of confirmatory batches (see question on GMP requirements for further guidance).

One specific feature of the 3DP process is the capacity of agilely producing a range of strengths from the same formulation, using a range of process parameters or conditions as per the validated printing design space. When several pre-defined dosage strengths (series of strengths) are applied for, a matrixing or bracketing approach may be acceptable for 3DP process validation, focusing on certain pre-determined and justified strengths. This is also valid for finished product stability studies (see for further reference ICH Q1D, VICH GL45 and EMA guideline on process validation).

Control Strategy

A control strategy should be established to ensure consistent quality, safety, and efficacy of the product. In particular, the applicant/manufacturer should justify the proposed control strategy approaches for in-process control testing and for release of the pharma ink and the finished product. The following points should be considered:

- Specifications for release and shelf-life for the pharma ink and the finished product should be proposed in compliance with relevant EMA guidelines and EP monographs, if applicable.
- The specification tests of the medicinal products manufactured by 3DP are, in general, the same as of the traditional solid oral pharmaceutical forms, e.g. assay, content uniformity, impurities, residual solvents, microbiological quality, disintegration and/or dissolution (see for further reference ICH Q6A and VICH GL39).
- The use of non-destructive techniques such as NIR and Raman spectroscopy during the manufacturing process should be considered, especially for small batch sizes with limited testing capacity. The control capability of the 3D printers (e.g. with pressure sensors for mass control, balance, NIR and Raman) could be used to monitor the printing process and discard non-conforming dosage units in real-time.
- Based on the data collected during the manufacturing process, an appropriate combination of equipment design and configuration and CPPs, together with pre-defined material attributes, may provide greater assurance of product quality than end-product testing and, as such, be an integral part of the control strategy (see for further reference EMA Guidelines on Real Time Release Testing and Parametric Release).

4. What GMP requirements are relevant and applicable to support the use of 3DP in pharmaceutical manufacturing?

The 3DP manufacturing process generally consists of the following activities:

- Equipment design/qualification/validation (including 3D printing software).

- Manufacture of the intermediate cartridges/syringes.
- Printing process, including process control.
- Quality control testing.
- Batch certification and release.

Equipment

The 3D printer, including the computerised systems, as for any other manufacturing equipment, should be designed, located, qualified and maintained to suit its intended purpose in accordance with EU GMP (see for further reference EU GMP Chapter 3, Annexes 11 and 15, and Commission Implementing Regulation 2025/2091 Chapter IV, and Annexes IV and V).

A program of maintenance/calibration is required to ensure the good performance of the 3D printer, and this should be in line with the recommendations by the 3D printer manufacturer. In turn, the finished product manufacturer should ensure that the maintenance program is performed. In the event that maintenance activities are outsourced to the 3D printer manufacturer, a contract agreement detailing the respective responsibilities should be in place.

A preventive maintenance plan should be established to ensure optimal condition of use and the smooth operation of the 3D printer, and avoid unintentional deviations, equipment malfunctions and production interruptions. Monitoring systems must be in place to detect and resolve potential issues quickly.

Pharmaceutical materials (Cartridges/Syringes)

Usually, for 3DP, the pharmaceutical materials (active substances, excipients, or their mixtures) are presented in cartridges or syringes.

Cartridges/syringes can be manufactured directly by the finished product manufacturer conducting the 3D printing or received ready-to-use from a different manufacturer. The preparation of the active substance(s)/excipient(s) mixture and its filling into the cartridge are considered part of the finished product manufacturing process (intermediate manufacturing), and compliance with Part I of EU GMP guidelines and Commission Implementing Regulation 2025/2091 for products is required by any manufacturer conducting this activity (see references below).

The selection, qualification, approval and monitoring of suppliers of active substances, excipients, starting materials or pharmaceutical containers should be performed according to the EU GMP (see for further reference the Chapters 4, 5 and 7 of the EU GMP, and Chapters V, VI and IX of the Commission Implementing Regulation 2025/2091), and the level of supervision should be proportionate to the risks posed by the individual materials, taking into account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product.

Manufacturing process

The amount of information received from the manufacturer of the 3D printer should be sufficient for the medicinal product manufacturer to fully understand the functioning of the equipment and to identify the process parameters critical for the product.

The application of quality risk management (QRM) to the 3D printing process can help to proactively identify and control potential quality issues, and to ensure the expected quality of the 3D printed products is delivered to the patients. QRM should be integrated into existing operations and documented appropriately (see for further reference ICH Q9 R1).

The high accuracy of deposition (resolution) is an inherent feature of 3DP technology, which is an advantage over other traditional manufacturing methods. The defined process parameters should be monitored and, where necessary, controlled to ensure the process produces products with the desired quality within the validated ranges (see also the pharmaceutical development paragraph in question on quality requirements above for further details).

At every stage of manufacturing, products and materials should be protected from microbial and other contamination, including cross-contamination. It should be prevented by appropriate design and maintenance of the premises and equipment, and use of cleaning procedures of validated effectiveness. Risk minimization measures should be proposed, such as the use of disposable material in contact with the product. Dedicated premises or containment may be necessary, according to the QRM, in case of highly active components, toxic or sensitizing materials handling.

Appropriate training should be provided for the personnel according to Chapter 2 of the EU GMP and Chapter III of the Commission Implementing Regulation 2025/2091, considering also the involvement of the 3D printer manufacturer in the personnel training, e.g. file conversions maintenance, equipment uses.

Outsourced activities should be appropriately defined, agreed and controlled, according to Chapter 7 of the EU GMP and the Chapter IX of the Commission Implementing Regulation 2025/2091, to ensure the outsourced activities are carried out successfully, e.g. 3D printer manufacturer qualification, maintenance, software update, and modifications to the equipment.

Qualification and validation

It is a GMP requirement that pharmaceutical product manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process (see for further reference Annex 15 of EU GMP guidelines and the Annex V of the Commission Implementing Regulation 2025/2091). Use of QRM should ensure that the manufacturer's efforts are focused on the areas of highest risk by addressing CPPs and potential failure modes.

It is expected that the 3D printing process (e.g. printing parameters of speeds, temperatures) is validated. The 3D printer, if used to manufacture medicinal products, should be considered pharmaceutical production equipment and should be adequately qualified. Both qualification and validation activities should be completed in accordance with annex 15 of EU GMP guidelines and Annex V of the Commission Implementing Regulation 2025/2091 (see references below).

The 3D printing equipment should be used within the recommended settings/conditions of its manufacturer/supplier, unless the in-house operating mode has been fully validated. It is acceptable that 3D printer qualification activities are carried out by the manufacturer/supplier of the printer. Equipment knowledge and understanding from the 3D printer manufacturer are also important for the finished product manufacturer/user for building their own knowledge to support the equipment and process validation and demonstrate that the printing process is capable of consistently producing medicinal products that meet pre-determined quality and performance standards. The collaboration between the users and the pharma ink/printer suppliers is considered also relevant in the case of PAT tools implementation. In the event that qualification/validation activities are outsourced to the 3D printer manufacturer, a contract agreement should be in place (see for further reference Chapter 7 of the EU GMP and the Chapter IX of the Commission Implementing Regulation 2025/2091).

The 3D printer should be cleaned and decontaminated depending on the products being manufactured. The related cleaning processes should be validated, and appropriate procedures should be established. The cleaning of the empty cartridges/syringes should also be validated (see for further reference Chapter 4 and Annex 15 of the EU GMP, and the Chapter V and Annex V of the Commission

Implementing Regulation 2025/2091). The use of dedicated/single-use cartridges/syringes could reduce risks of contamination.

A 3D printer is a fully computer-driven system, and compatibility between printer and software is critical to the quality of the final medicinal product. The computer validation should be carried out according to the Annex 11 of the EU GMP guidelines and the annex V of the Commission Implementing Regulation 2025/2091 (see references below), and should include, among others, data integrity management, 3D model design, qualification and validation, qualification of the file transfer to the printer, software validation and software update management. In case Artificial Intelligence (AI) is used in the 3DP, the Annex 22 of the EU GMP guidelines and the EMA Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle should be considered (see references below).

5. References

EMA Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017 Rev. 2): Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials - Rev. 2

ICH guideline Q8 (R2) on pharmaceutical development (EMA/CHMP/ICH/167068/2004): Q8 (R2) Step 5 Pharmaceutical Development

ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances: Q 6 A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

VICH GL39 Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances EMEA/CVMP/VICH/126623/2005

ICH guideline Q9 (R1) on quality risk management: ICH guideline Q9 (R1) on quality risk management

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EMA Questions and answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters (EMA/CHMP/CVMP/QWP/354895/2017): Questions and Answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters

EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1): Guideline on process validation for finished products - information and data to be provided in regulatory submissions

EMA Guideline on Real Time Release Testing (formerly Guideline on Parametric Release) (EMA/CHMP/QWP/811210/2009-Rev1): Real Time Release Testing guideline

EMA Guideline on Parametric release (EMA/CVMP/QWP/339588/2005 – Rev 1): Guideline on Parametric release

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en

Commission Implementing Regulation (EU) 2025/2091 of 17 October 2025 laying down good manufacturing practice for veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council: Implementing regulation - EU - 2025/2091 - EN - EUR-Lex

Commission Implementing Regulation (EU) 2025/2154 of 17 October 2025 laying down good manufacturing practice for active substances used as starting materials in veterinary medicinal products in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council: Implementing regulation - EU - 2025/2154 - EN - EUR-Lex

EMA Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle: Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle_240903