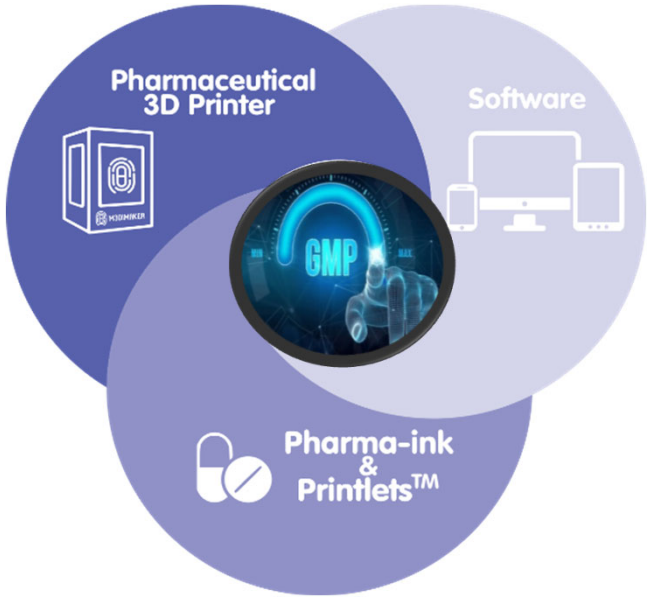


Colloque d'experts de la Pharmacopée Swissmedic 18 Octobre 2024

swissmedic

Regulatory & Validation Aspects of Pharmaceutical 3D Printing

F. Sadeghipour

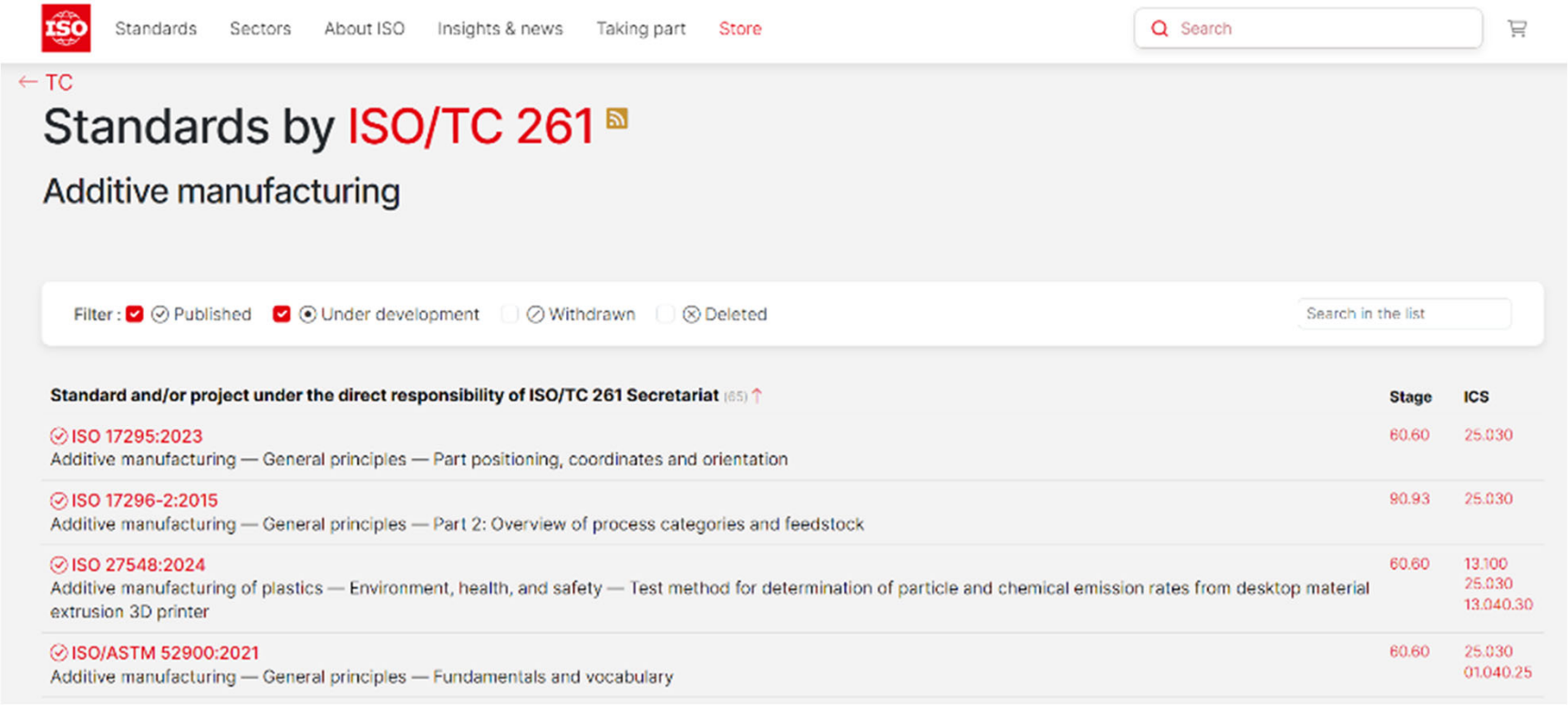
18.10.2024

Advantages and limitations in pharmacies

Advantages	Limitations
Customization and personalization—3D printing allows for the production of customized and personalized products that are tailored to the specific needs of individual patients to improve the effectiveness and safety of the treatment [59,60,61].	Regulation and quality control—Regulatory and quality control issues must be addressed to ensure the safety and efficacy of 3D-printed pharmaceutical products [59,62].
Complex structures and geometries—3D printing allows for the production of complex structures and geometries that are not possible with traditional manufacturing methods and that can enable the development of new and innovative drug delivery systems [1,13,14,26,63].	Material selection and compatibility—The selection of materials suitable for use in 3D printing in the pharmaceutical industry is limited, and compatibility issues exist with certain drugs or formulations [59].
Cost and efficiency—3D printing can potentially reduce the cost and increase the efficiency of the manufacturing process by enabling the production of small batches of products on demand and reducing the need for large-scale production and inventory management [63,64].	Scaling up production—Technical challenges exist in scaling up the production of 3D-printed products to meet the demand of the market [59,65].

Pharmaceutics 2023, 15, 1877. https://doi.org/10.3390/pharmaceutics15071877

Regulatory for Medical Devices 3D printers



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Standards by ISO/TC 261

Additive manufacturing

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Standard and/or project under the direct responsibility of ISO/TC 261 Secretariat (65)	Stage	ICS
ISO 17295:2023 Additive manufacturing — General principles — Part positioning, coordinates and orientation	60.60	25.030
ISO 17296-2:2015 Additive manufacturing — General principles — Part 2: Overview of process categories and feedstock	90.93	25.030
ISO 27548:2024 Additive manufacturing of plastics — Environment, health, and safety — Test method for determination of particle and chemical emission rates from desktop material extrusion 3D printer	60.60	13.100 25.030 13.040.30
ISO/ASTM 52900:2021 Additive manufacturing — General principles — Fundamentals and vocabulary	60.60	25.030 01.040.25

- Classical ISO regulations as ISO 13485 (Medical device manufacturers)

https://www.iso.org/committee/629086/x/catalogue/

Regulatory for Medical Devices 3D printers

FDA U.S. FOOD & DRUG ADMINISTRATION

← Home / Medical Devices / Products and Medical Procedures / 3D Printing of Medical Devices

3D Printing of Medical Devices

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3D Printing of Medical Devices

Medical Applications of 3D Printing

Process of 3D Printing Medical Devices

FDA's Role in 3D Printing

3D Printing Medical Devices at the Point of Care: Discussion Paper

Overview

3D printing is a type of additive manufacturing. There are several types of additive manufacturing, but the terms 3D printing and additive manufacturing are often used interchangeably. Here we will refer to both as 3D printing for simplicity.

3D printing is a process that creates a three-dimensional object by building successive layers of raw material. Each new layer is attached to the previous one until the object is complete. Objects are produced from a digital 3D file, such as a computer-aided design (CAD) drawing or a Magnetic Resonance Image (MRI).

The flexibility of 3D printing allows designers to make changes easily without the need to set up additional equipment or tools. It also enables manufacturers to create devices matched to a patient's anatomy (patient-specific devices) or devices with very complex

https://www.fda.gov/medical-devices/products-and-medical-procedures/3d-printing-medical-devices

Regulatory for Medical Devices 3D printers

REGULATIONS

REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

(Text with EEA relevance)

Core Legal Challenges for Medical 3D Printing in the EU

by Ante B. V. Pettersson [1,2,*], Rosa Maria Ballardini [3], Marc Mimler [4], Phoebe Li [5], Mika Salmi [6], Timo Minssen [7], Ian Gibson [8] and Antti Mäkitie [1,9,*]

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745

https://www.mdpi.com/2227-9032/12/11/1114#:~:text=We%20performed%20an%20analysis%2C%20using,property%20rights%2C%20and%20data%20protection.

Regulatory for Medical Devices 3D printers

- Medical devices printing
  - MD classification
- Industrial printing (Serial and batch printing)
  - Legally marketed 3D printed devices are subject to the same regulatory requirements to which similar devices created without 3D printing are subject, including Quality Systems (QS) regulations
- Printing at Point of care
  - PoC 3D printing centers should be particularly mindful of when creating their own "best practices."
    - Monitoring, maintenance protocols, and control of process parameters
    - Materials
    - Support material
    - Layering and Meshing
    - Build paths, …

Technical Considerations for Additive Manufactured Medical Devices. https://www.fda.gov/media/97633/download. Accessed 14 December 2021

Why Regulations for Drugs 3D Printers?

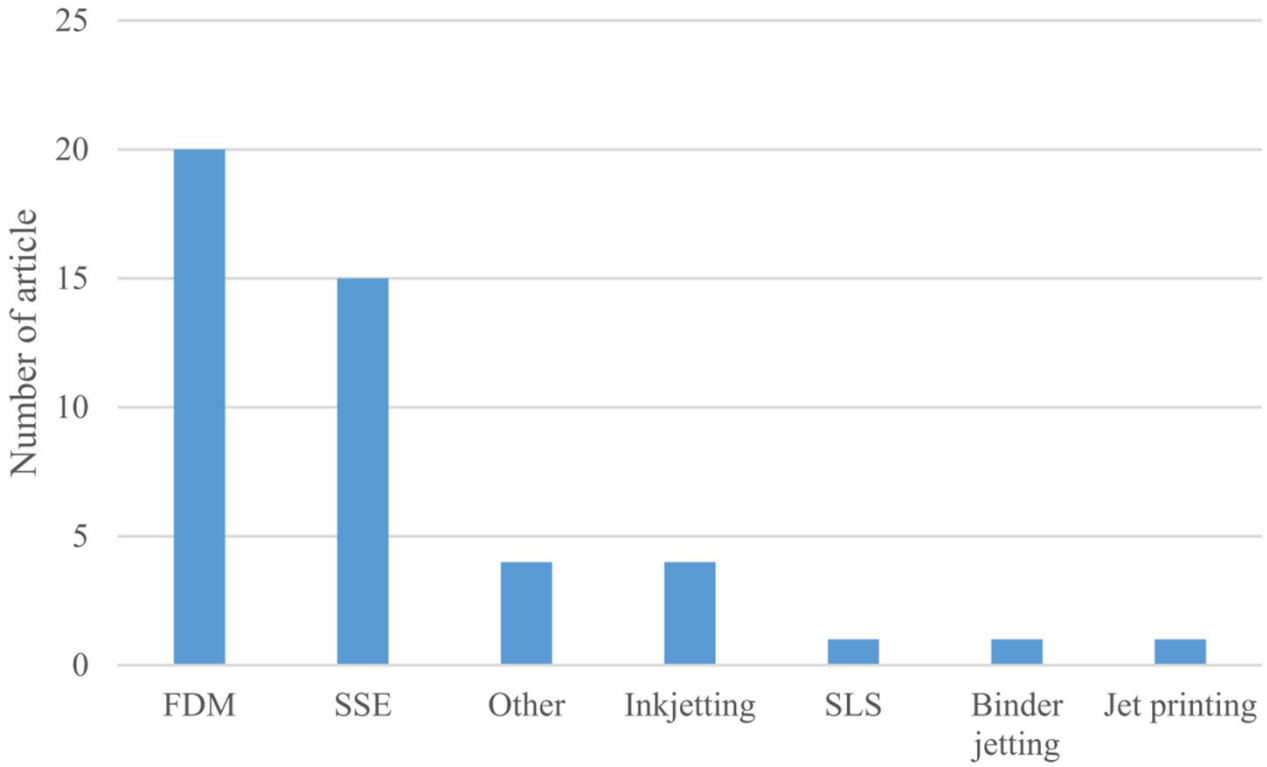


Fig. 3. Number of research articles on pediatric oral solid form per 3D printing techniques.

FDM : Fused Deposition Material
SSE : Semi-Solid Extrusion
SLS : Selective Laser Sintering

International Journal of Pharmaceutics; Volume 662, 5 September 2024, 124402; https://doi.org/10.1016/j.ijpharm.2024.124402

Regulatory for Drugs 3D Printers

Baseline considerations

- High resolution printing to ensure dosage accuracy,
- High quality and purity materials must be of to guarantee safety and efficacy
- Pharmaceutical-grade raw materials
- Availability of sufficient materials for 3D printing
- Compatibility of printing excipients (ink): the medicine, biocompatible, biodegradable,
- Not generate potentially toxic substances during the printing process
- Quality control and safety to verify that the printed medications fit the appropriate requirements
- Stability over time and its degradation due to heating, pressure, and solvent during the printing process
- The training and education of healthcare workers, including pharmacists on how to use 3D printing technology safely and effectively

Pharmaceutics 2023, 15, 1877. https://doi.org/10.3390/pharmaceutics15071877

Regulatory for Drugs 3D Printers

- The printer will need to comply with the applicable rules and harmonized standards for machinery (Directive 2006/42/EC), whereas the medical devices it produces will need to comply with the applicable medical device rules (Regulation (EU) 2017/745 (EU MDR)).
- No regulations have provided recommendations or guidelines for the use of 3D printing in pharmaceutical production.
- Risk assessment by 3D printers Manufacturers to ascertain the health and safety requirements applicable to the machinery (Machinery Directive 2006/42/EC)
- USFDA has not issued any guidance or regulations regarding the use of 3D printing in drug manufacturing.
- Similarly to the USFDA, the EMA has not issued any regulations regarding 3D-printed dosage forms.
- **Characterization of the "printed" tablets, gums, etc.** :
  - **Identical to any other solid dosage form**

Pharmaceutics 2023, 15, 1877. https://doi.org/10.3390/pharmaceutics15071877

3D Printers Qualification

- **Business as usual**
  - **DQ??**
  - **IQ**
  - **OQ**
  - **PQ**

Table of contents : Site acceptance tests

3D Printer, Pharmacy, Lausanne univeristy hospital

3D Printers Qualification

- **DQ**
  - Identify specific needs for personalized medications in your hospital pharmacy
  - Determine required dosage forms, drug combinations, and production volumes
  - Ensure the printer can meet pharmaceutical standards and regulations

  - ***Engineering tasks***
  - ***Out of scope for pharmacies***
  - ***Some research works in hospital pharmacies***

3D Printers Qualification

- **IQ**
  - Running test jobs to demonstrate performance equivalence before and after shipment
  - Completing necessary safety checks and machine conformity tests

3D Printers Qualification

- **IQ**

Check the CE-label of the scale is in place. Write the serial number and scale model to the reserved space. Note: The printer is expected to be fully installed and the access to the scale CE-label is limited. One can use the photo or notes made during installation to verify the CE-label content.
Scale CE-label is in place and the scale model is either Kern PES 620-3M or Kern PEJ 620-3M Check the scale serial number matches the serial number in FAT.

Check the CE-label of the printer is in place. Write the serial number to the space reserved.
Printer CE-label is in place and it is for Pharma Printer with model number PP021. ✓ Check the printer's serial number matches the serial number in FAT.

3D Printers Qualification

- **IQ**

Check the printer and the scale visually inside and outside. Pay special attention to following items: - Transportation supports are removed as per installation instructions ✓ - Heating jacket should be removed, checked and reinserted ✓ - Side doors are locked and inaccessible ✓ - Door and top hood can be opened and closed without issues ✓ - Printer drive belt is intact ✓ - Slide bars are clean and oiled ✓ - Metallic protecting plate for the scale is properly installed with screws in place ✓ - Power cord is in pristine condition and locked to the printer socket ✓	Check the following items are delivered with the printer: - Five syringes ✓ - Five syringe caps ✓ - One silicone mat ✓
No scratches, or any damage can be seen.	All materials have been delivered and are ready to be used.

3D Printers Qualification

- **IQ**

Check the scale is installed properly to its place.
The weighing pan must not touch the metallic cover even when pressed slightly. ✓ The metallic cover is properly installed. ✓ There is no debris on the scale pan. ✓

Calibrate the scale according to the scale's manufacturer's instructions.
The weighing pan must not touch the metallic cover even when pressed slightly. ✓ The metallic cover is properly installed. ✓ There is no debris on the scale pan. ✓

3D Printers Qualification

- **OQ**
  - Building test jobs with static and/or dynamic test coupons
  - Demonstrating effectiveness and reproducibility of the printing process
  - Establishing a baseline for application design
  - Determining critical process parameters through Design of Experiments (DOE)

3D Printers Qualification

- **OQ**
  - **Scale operations**
  - **Device software functionality**
  - **Test order print**

Enter the main screen of the printer. Hit the emergency power off button. Wait 5 seconds. Release the button. Wait for the printer to start.
The EPO button must cut power off immediately. Releasing the button restarts the printer.

Prepare the equipment for the coming test. Fill the syringe to 50ml with room temperature water. Insert the nozzle to the syringe. Place the priming container to its place, front left side. Place the extrusion container to its place, on top of the scale. Move to the debug screen by pressing the CurifyLabs' logo eight times. Then press "config" in the newly appeared buttons.
The printer should be on, in the debug screen. The heating jacket should be empty.

Print all the three orders (300 mg, 400 mg, and 500 mg) with water. Note: One needs to re-enable the orders after one is printed.
When the printer is printing, check visually the following things: - The scale tares itself in the start. - The printhead moves smoothly. - The priming extrudes water three times. - There will be 16 extrusions on the scale per printing round. From the 3x16 printed tablets, 3 can be out of the +- 5 % range. If there's 3 to 6 out of range, the test can be redone. If there's more than 6 out of range, contact CurifyLabs and start seeking corrective actions and root cause for the issue.

3D Printers Qualification

- **PQ**
  - Conducting first article inspection and testing
  - Calculating process capabilities
  - Implementing statistical process control strategies
  - Demonstrating repeatable, reproducible, and consistent part performance

PQ or Specific Drug Production Procedure validation ????

PQ : Printing Methods & Excipients

Pharm Res (2018) 35: 176

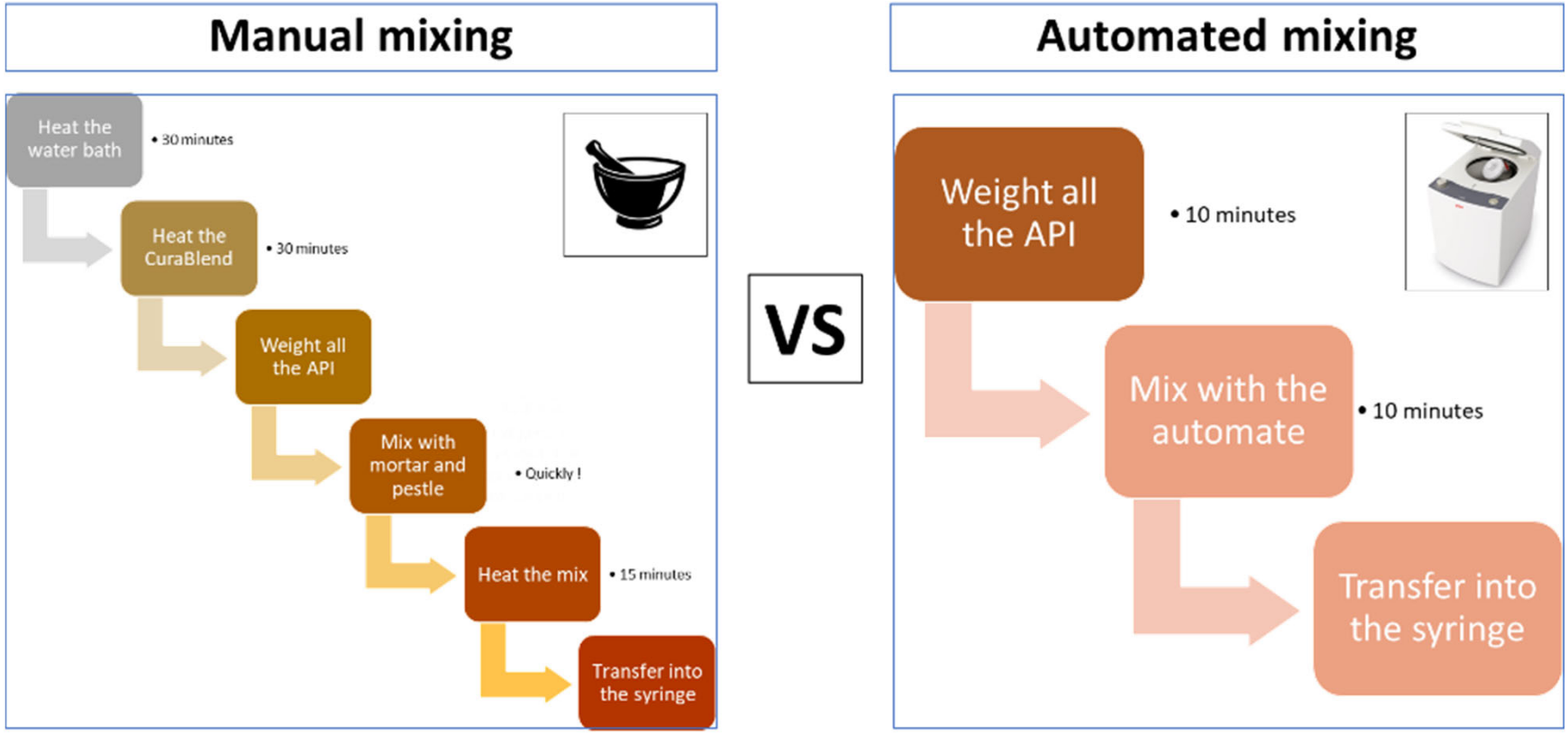
PQ : Printing Methods & Excipients

CuraBlend ® Composition

Ingredients	Quality	Amount (mg/tablet) for 500 mg **tablet**	Paediatric suitability
Aq.purif.	Ph.Eur.	213.35	-
Xylitol	Ph.Eur.	101.85	Maximum daily exposure: 360 mg (FDA Database) Threshold: 10 g (EU labelling of medicinal products) (May have a laxative effect.)
Gelatin (SiMoGel™)	Food grade (Complies with EU 853/2004 and EU 2073/2005)	62.11	Max potency per unit dose: 65 mg. Gelatin is an Excipient of Animal Origin hence TSE/BSE certificate is ensured for gelatin used in manufacturing of CuraBlend.
Cocoa butter	Ph.Eur.	61.20	Generally regarded as safe (GRAS), EFSA consumption levels: Toddlers: 0.2 g/kg body weight/day; Children: 0.8 g/kg body weight/day
Glycerol (85%)	Ph.Eur.	27.965	125 mg/kg body weight[4]
Maltodextrin (Maltrin® M180)	Food grade (Ph. Eur.)	21.15	292 mg/tablet[3]
Silicon dioxide	Ph.Eur.	6.15	254 mg[3] (maximum daily exposure)
Citric acid monohydrate	Ph.Eur.	2.34	7 mg /tablet [3]
Sodium citrate	Ph.Eur.	1.00	23 mg / dose[4]

PQ or Specific Drug Production Procedure validation

CHUV Example : Comparison of 2 protocols



A. Pierrot & al.; Development and validation of a production and a dosage methods of 3D printed tablets containing prednisolone; GERPAC Congress 2024

PQ or Specific Drug Production Procedure validation?

CHUV Example : Comparison of 2 protocols

Manual mixing

- Mix 1 = day 1
  - 200 mg x 25 tablets
  - 500 mg x 25 tablets
- Mix 2 = day 2
  - 200 mg x 25 tablets
  - 500 mg x 25 tablets
- Mix 3 = day 3
  - 200 mg x 25 tablets
  - 500 mg x 25 tablets
- Into blisters and labeled

Automated mixing

- Mix 1 = day 1
  - 200 mg x 25 tablets
  - 500 mg x 25 tablets
- Mix 2 = day 1
  - 200 mg x 25 tablets
  - 500 mg x 25 tablets
- Mix 3 = day 1
  - 200 mg x 25 tablets
  - 500 mg x 25 tablets
- Into blisters and labeled

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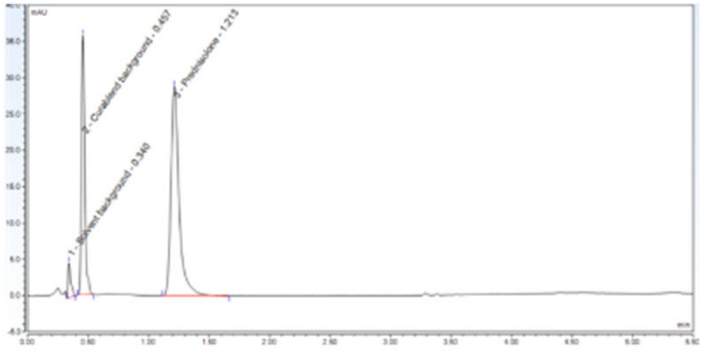
PQ or Specific Drug Production Procedure validation?

CHUV Example : Comparison of 2 protocols



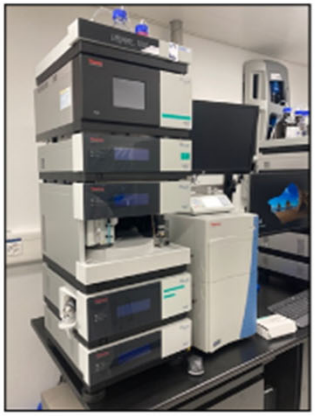
Mass uniformity

- Collection of masses of all tablets printed

Content uniformity

- Creation and validation of a method of analyses
  - In accordance with ICH Q2R2

- HPLC coupled with a diode array detector (DAD)
  - Column BEH C18 (Acquity™ Premier VanGuard™ FIT, 1.7 µm, 2.1 mm X 50 mm)
  - UV 280 nm
  - Mobile phase H2O/ACN



A. Pierrot & al.; Development and validation of a production and a dosage methods of 3D printed tablets containing prednisolone; GERPAC Congress 2024

Conclusions

- **3D Drug Printing :**
  - ***A Real Innovation***
- **Regulatory aspects :**
  - IQ & OQ :
    - ***Adaptation of the Qualification Protocoles as for every New Equipment or New Technology***
  - PQ and production procedure validation :
    - ***Boundaries still blurred***
- **GMP Aspects**
  - ***Business as usual with some adaptations***


THANK
YOU