

3D printing of pharmaceuticals

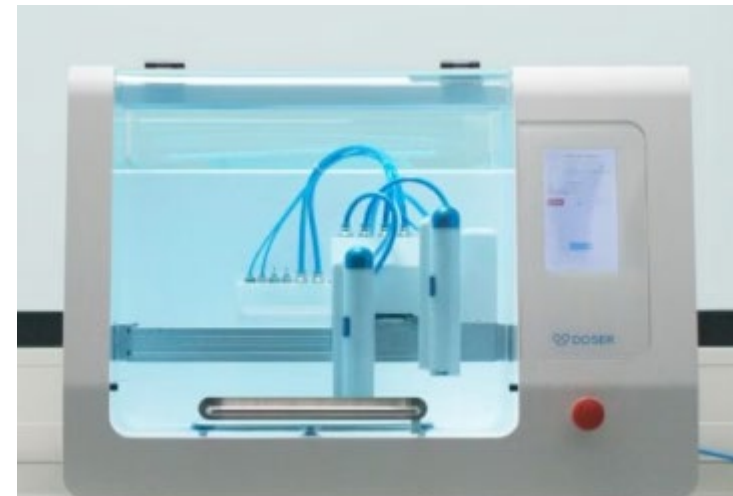
Kirsten Schimmel
 Department of Clinical Pharmacy and Toxicology,
 Leiden University Medical Centre, The Netherlands



11 APRIL 2024



Nationaal
 Farmaceutisch
 Kenniscentrum



Disclosure belangen spreker

Potentiële belangsverstrengeling	Geen / zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Samenwerking met Doser, zie onderzoeksproject hieronder
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk....	• GGG-project 838002663 Een 3D printer voor het gepersonificeerd doseren van geneesmiddelen • nvt • nvt • nvt

Short Intro of myself



Kirsten Schimmel (Hospital Pharmacist)

Head of GMP facility LUMC

(GMP license for clinical trial production since 2006)

Educational Director Master Pharmacy

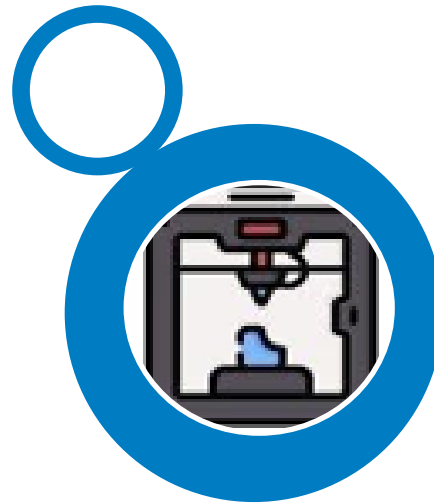
Since 2018: research 3D printing of pharmaceuticals

3D printing of pharmaceuticals

Why?



How?



What?



Why: personalized medicine



NOS Nieuws • Vrijdag 3 februari, 06:04



Medicatie op maat dankzij dna-profiel leidt tot minder ernstige bijwerkingen

Ernstige bijwerkingen van medicijnen nemen met 30 procent af als de dosering wordt afgestemd op het dna van patiënten. Dat blijkt uit een internationale studie onder leiding van het Leids Universitair Medisch Centrum (LUMC). Het is voor het eerst dat is aangetoond dat voorschrijven op basis van een dna-profiel ook echt effect heeft.



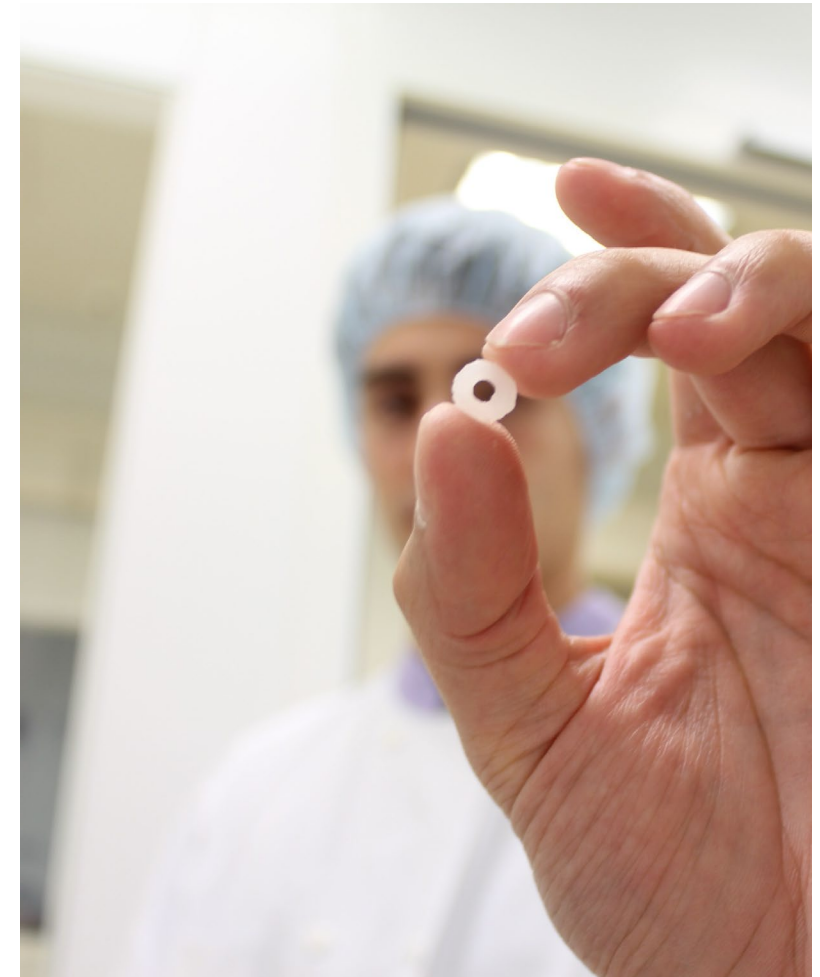
3D printing = flexibility



 Drug A



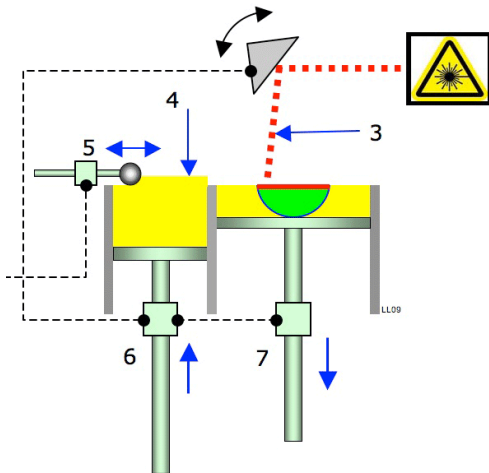
-  Geneesmiddel A
-  Placebo
-  Geneesmiddel B
-  Geneesmiddel C
-  Geneesmiddel D
-  Coating



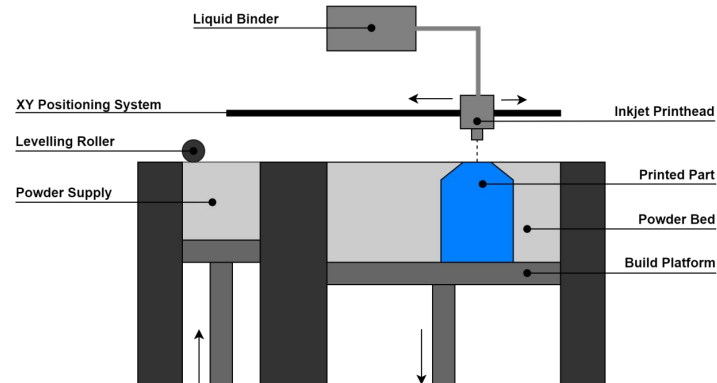
Techniques used in 3D pharma printing



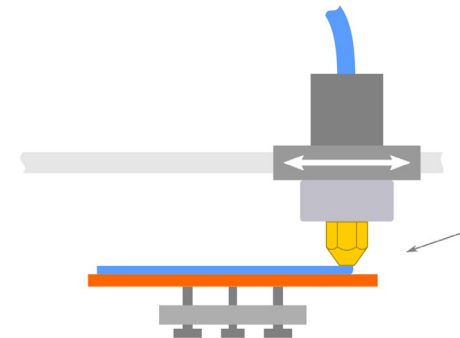
Laser based:
Selective laser sintering/
Stereolithography



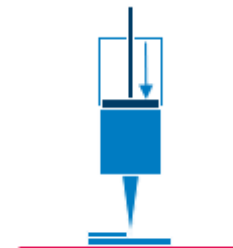
Inkjet:
Binder jet/Inkjet



Extrusion based:
Fused deposition modelling



Semi-solid extrusion



Printing process



Cartridge preparation

Step 1.
Melting and mixing

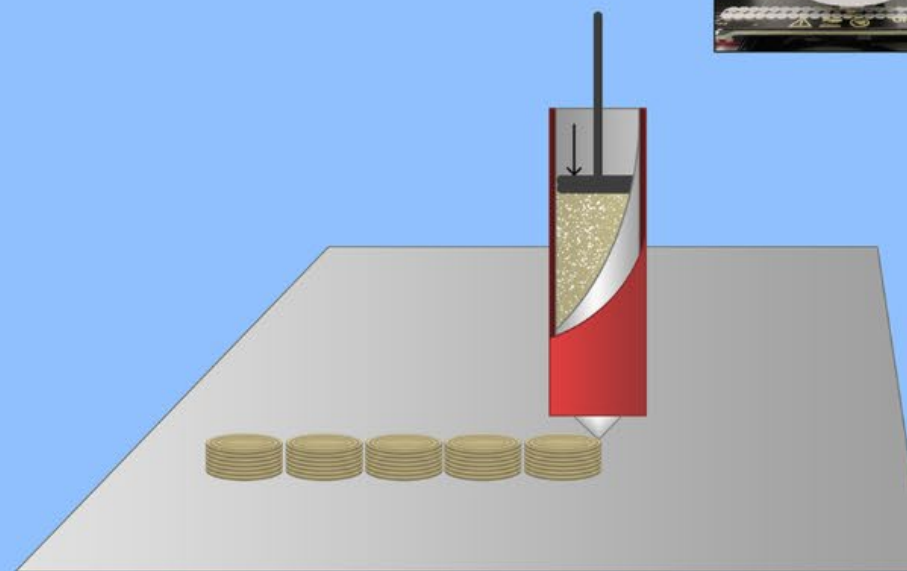
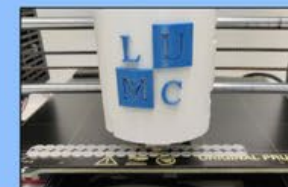


Step 2.
Filling cartridge



3D printing of the tablets

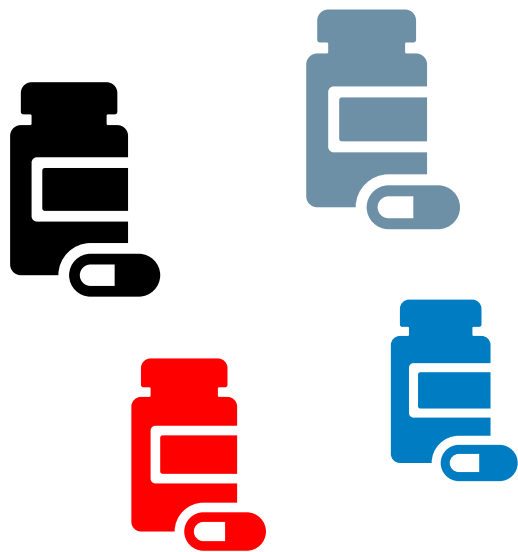
Step 3.
Printing tablets



Graphics by I. Lafeber

What needs to be done

Multiple formulations



Real time Quality control



Regulatory framework



What?



How far from clinic?



Requirements:

Formulation Platform

Intermediates available: inks, printlets

Challenges:

Concentration Range

Interaction API with excipients

Development time



SSE printer

Formulation development users/company



Different printing techniques

Formulation development users/company



SSE printer

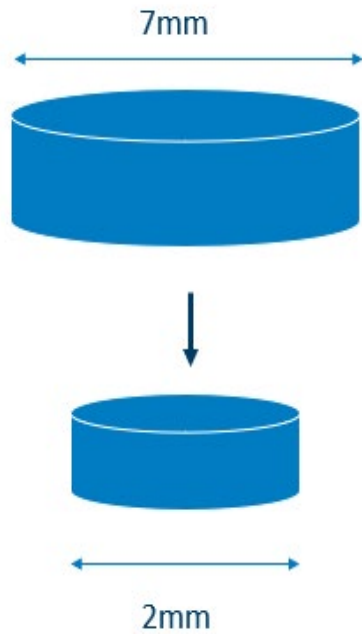
Excipient base by company, user adds/mixes API



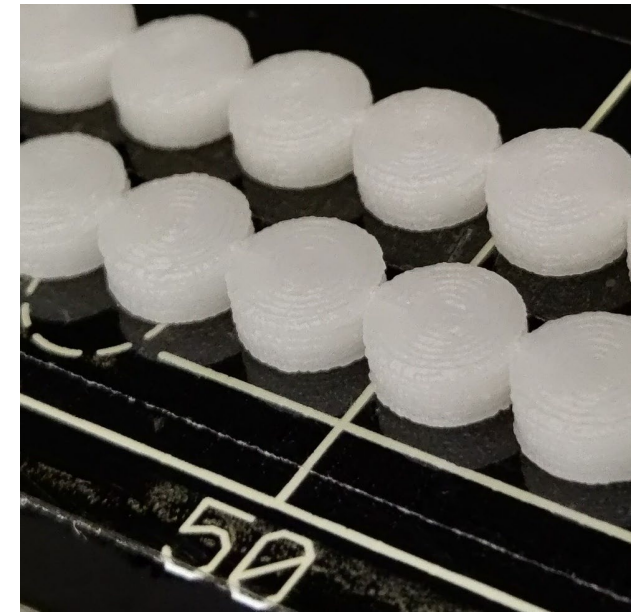
HME printer

Granules with API by company and/or development by user

What can currently be printed in LUMC?

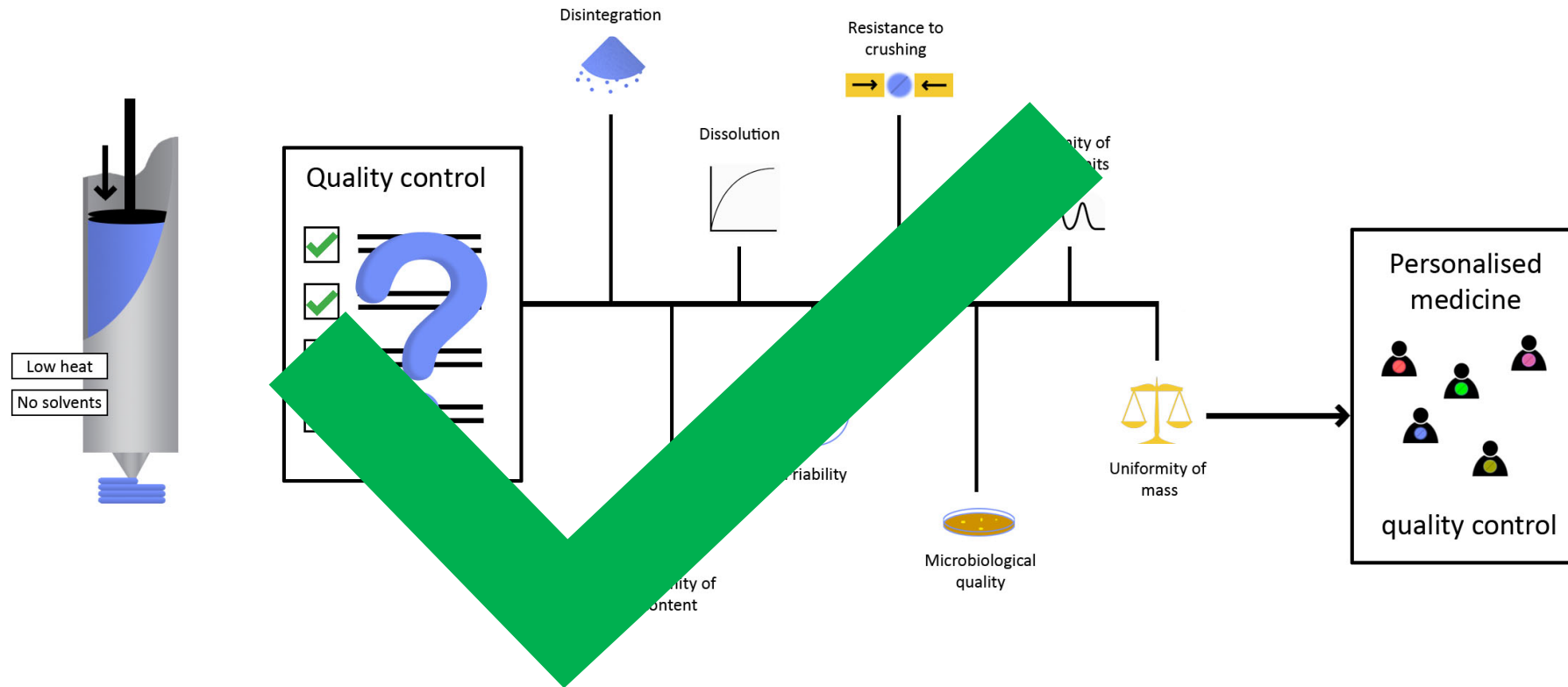


- Furosemide (2 mg; 10 mg)
- Sildenafil (4 mg; 7 mg; 10 mg)
- In development:
- Mexiletine, amlodipine....
- Polypill
- Mini tablets



3D printed tablets as good as commercial tablets?

Research: Quality Control



Graphics by I. Lafeber

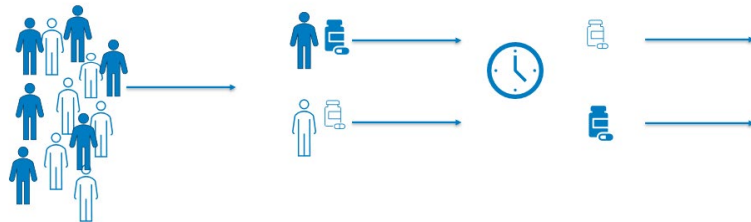
Do 3D printed tablets behave the same as conventional tablets?

Research: Pharmacokinetic



Clinical trial executed in LUMC:

'A randomized, open-label, single dose two-way cross-over pharmacokinetic study of 3D-printed sildenafil tablets compared to the originator sildenafil tablets in healthy adults'



Clinical Pharmacology & Therapeutics

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Development and Bioequivalence of 3D-Printed Medication at the Point-of-Care: Bridging the Gap Toward Personalized Medicine

Maryam Lyousofi, Iris Lafeber, Dinemarie Kweekel, Brenda C. M. de Winter, Jesse J. Swen, Paul P. H. Le Brun, Erica C. M. Bijleveld-Olierook, Teun van Gelder ... [See all authors](#) ▾

First published: 10 February 2023 | <https://doi.org/10.1002/cpt.2870>

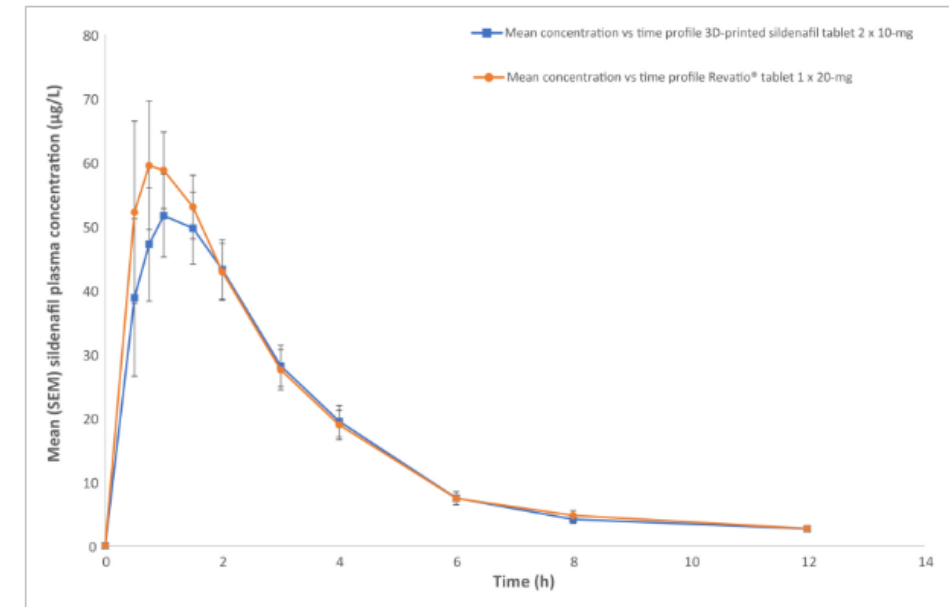


Figure 4

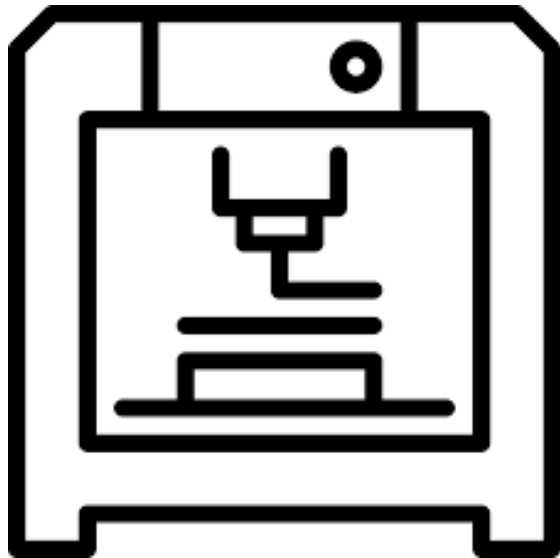
[Open in figure viewer](#) | [PowerPoint](#)

Mean plasma sildenafil concentration-time profiles ($n = 12$) of Revatio® and the 3D-printed tablets over 12 hours following a single 20 mg dose. Error bar represents standard error of the mean.

Current research: Integration of PAT tools



PAT = process analytical technology: Goal: dose prediction



Spectroscopy:
homogeneity

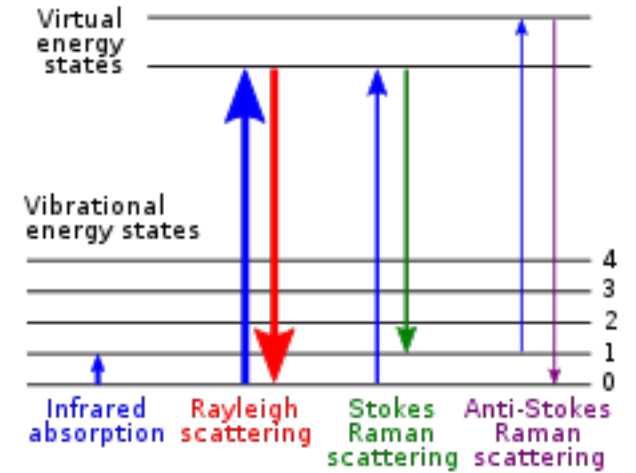
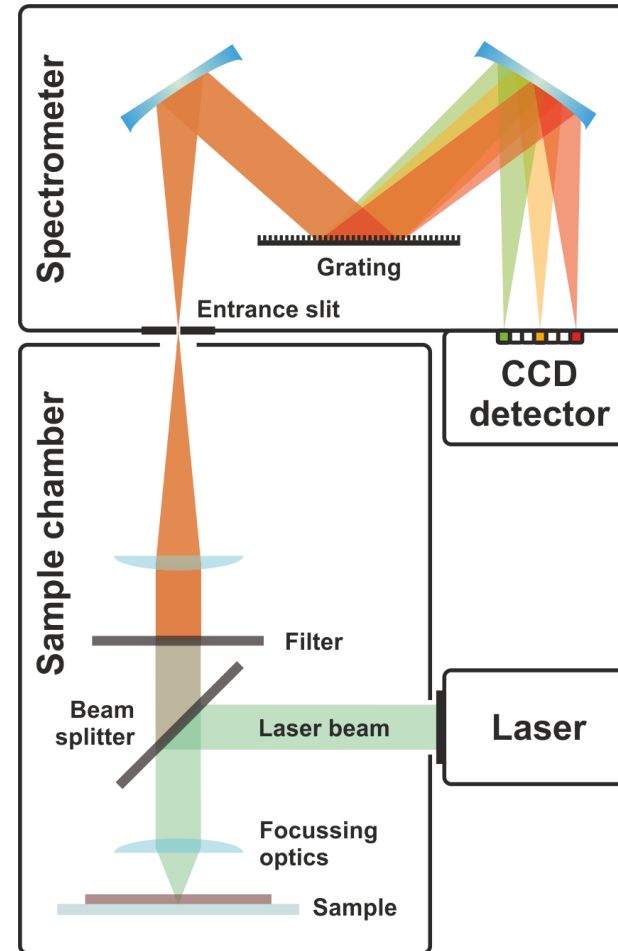
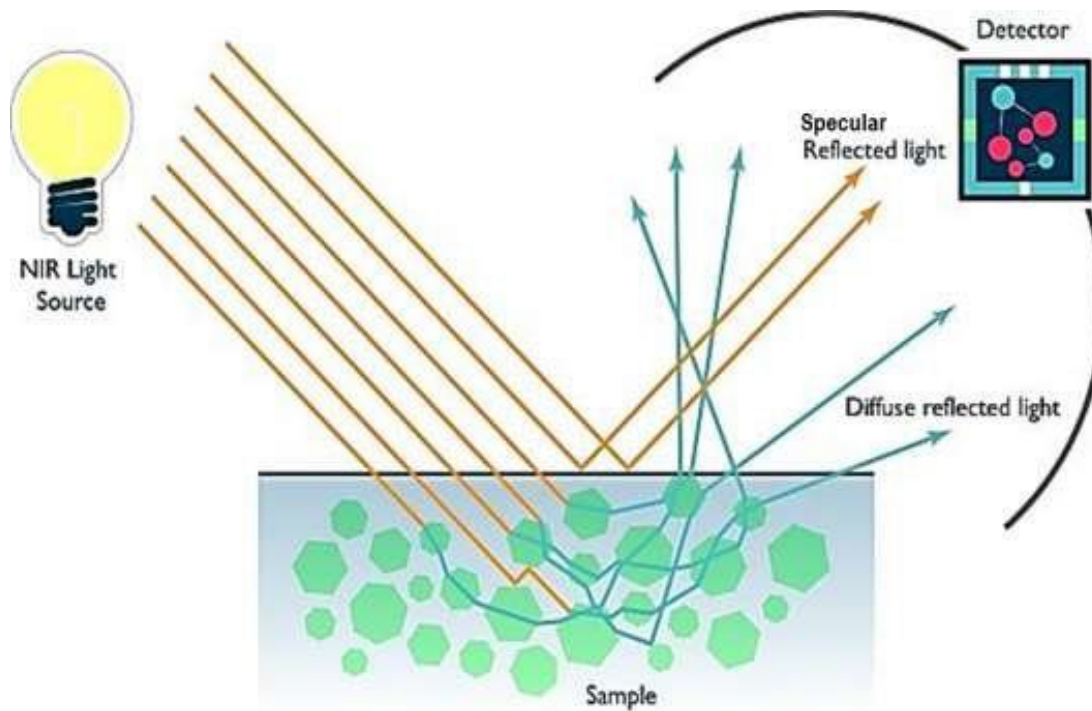
nIR- Raman:
homogeneity

Measurement of
extruded material

Machine Learning

nIR and Raman: Vibrational spectroscopy

- Near-infrared and Raman spectroscopy



Situating the 3D printer



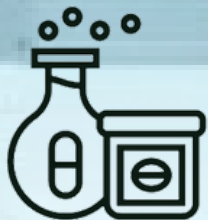
Local pharmacy
(including outpatient)



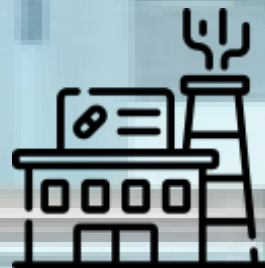
Hospital



Nursing home



Compounding pharmacy



Pharmaceutical industry



Patient's home

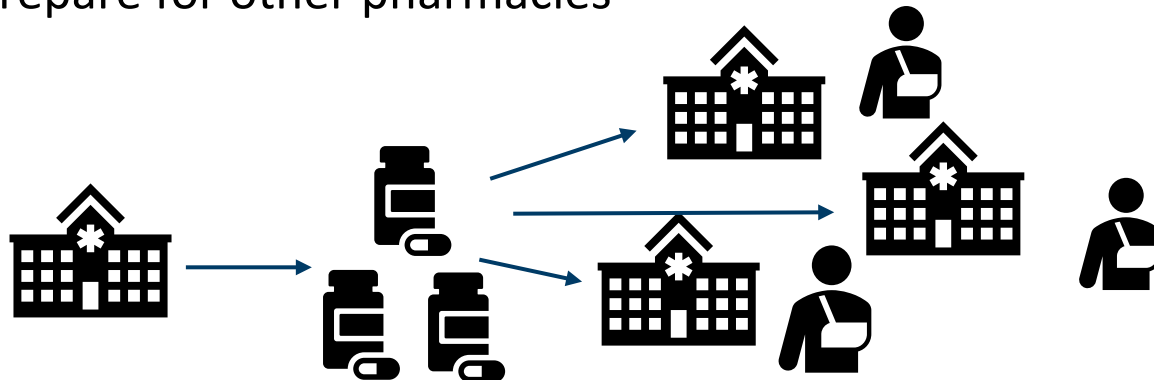


Differences in pharmacy preparation

Pharmacy preparation: each pharmacist can prepare medication for its own patients



In case of medical need and no licensed product available: compounding pharmacist is allowed to prepare for other pharmacies



Regulatory framework

Professional standards for pharmacy preparations:

Richtlijn bereiden: public pharmacies

GMP-Z: hospital pharmacies

add guidance where GMP is not suitable for process in hospital

Limits to nr of deliveries ('verstrekking in het klein')

National regulation: Circulaire Doorleveren:

GMP

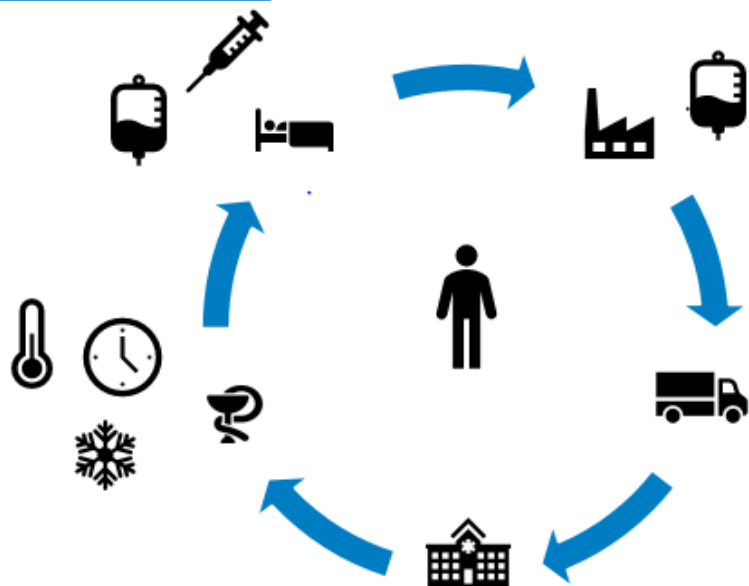
Compounding or Manufacturing License?



Personalized medicine = flexibility ≠ long registration

What if process is licensed?

CAR-T cells



What if printlet/
intermediate is licensed?



3D print process

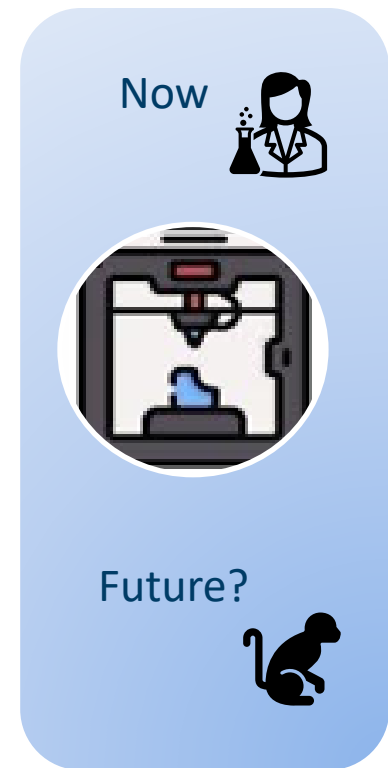


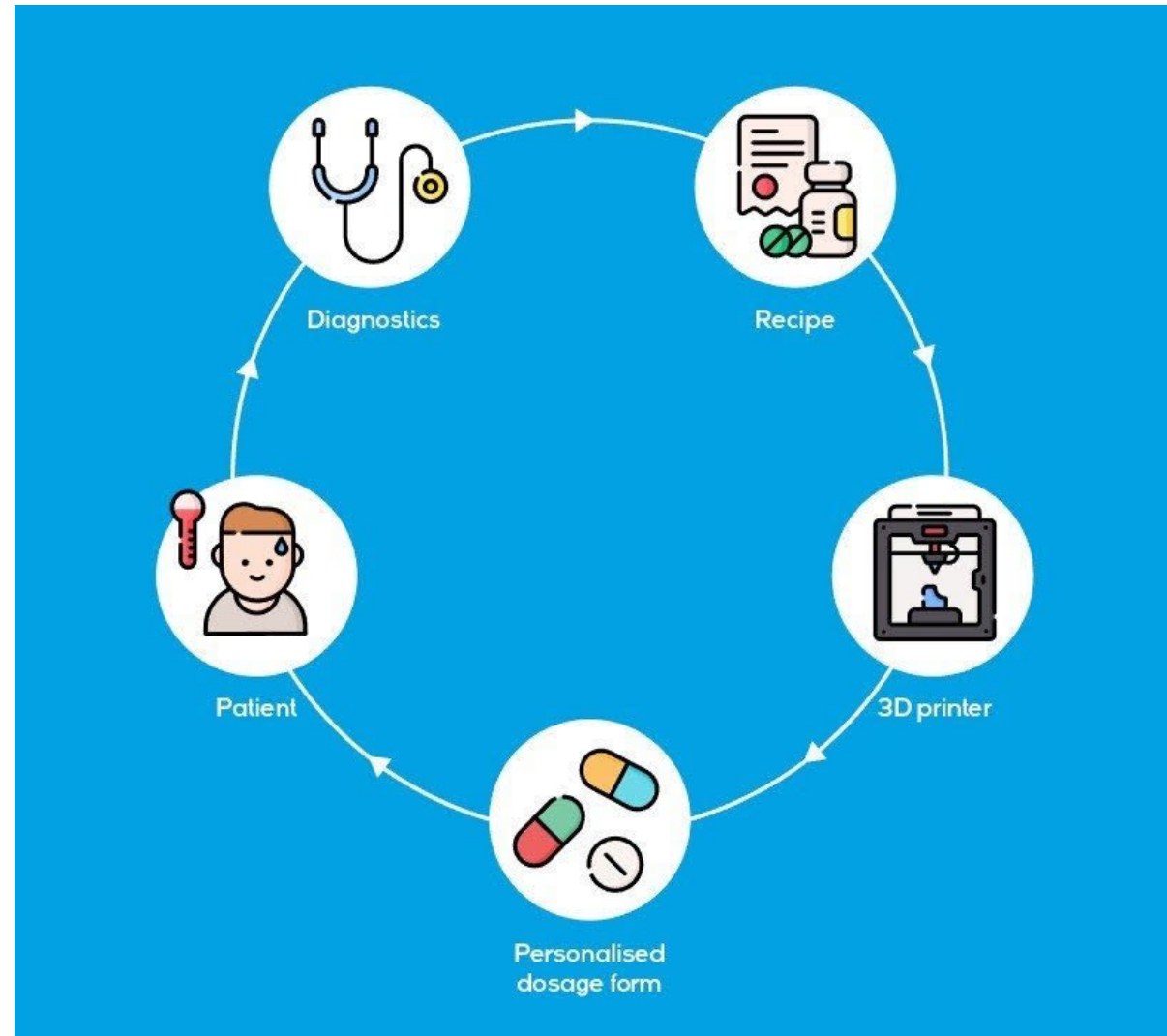
medication with
personal optimized dose





- Intermediates: printlets/inks/cartridges
 - In-process controls and production of test batches end product
 - Long shelf life
 - Storage conditions
 - Multiple use established
- Consistent production quality on-site
 - Design space added to validation file
 - Dosage range
 - Tablet shape and size
 - Shelf life
 - Real-time release testing





ACADEMIC PHARMA & 3D consortium



Nationaal
Farmaceutisch
Kenniscentrum



Iris Lafeber

Dinemarie Kweekel

Erica Bijleveld-Olierook

Aisha Ahmed

Lab technicians, students etc etc



LIÈGE université
**Center for Interdisciplinary
Research on Medicines**



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GRAND PARIS

TNO
innovation
for life

