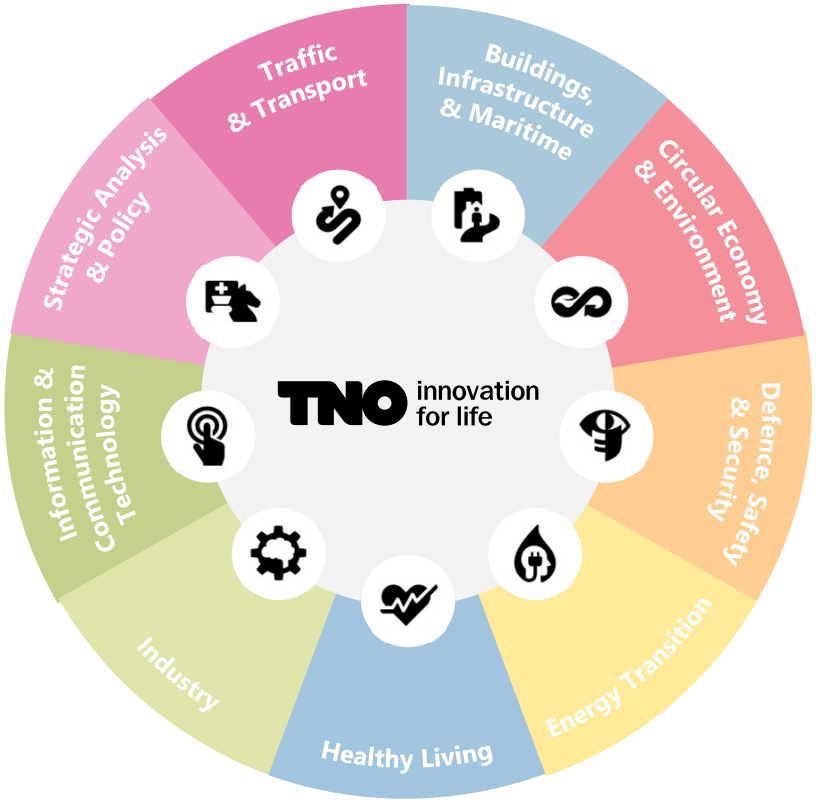
TNO 3D PHARMA PRINTING

BID 2022 TEL AVIV

3D Pharma printing @ TNO, 2022

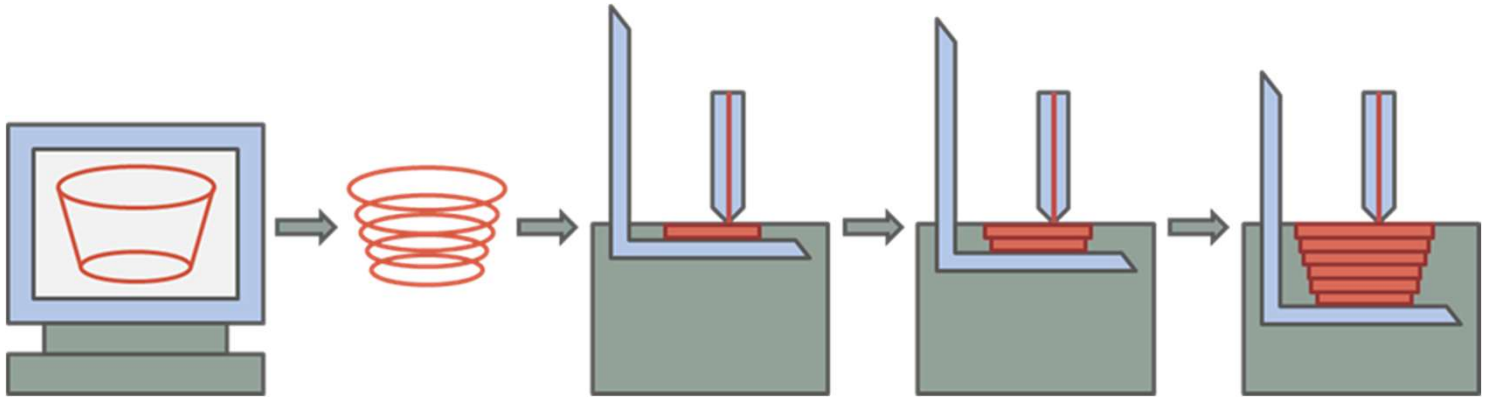
TNO
WHO WE ARE AND WHAT WE DO

- Largest independent contract research and innovation organization in The Netherlands, est. 1932
- Over 3400 researchers active in 9 Units
- Positioned between Universities and commercial companies
- **Mission:** Apply scientific knowledge to boost the innovative strength of our partners
- *Active in 3D printing for 30+ years*



WHAT IS 3D PRINTING?

HOW IT IS BEING USED ALREADY.



General Electric invests 100 million euros into German 3D printing site

General Electric (GE) is continuing to focus its gaze squarely on the EU 3D printing industry, with a game-changing investment of 100 million euros ($109 million USD) into a newly acquired production site in Lichtenfels, Germany.

Just last year, the multinational producer of jet engines, power plants, and other industrial equipment poured a total of $1.3 billion into Concept Laser, a privately held German 3D printing firm, and Swedish 3D printer-manufacturer Arcam. The strategic move secured GE majority shares in both companies, cementing its position as a global leading player in additive manufacturing.

Adidas to mass-produce 3D printed Futurecraft 4D shoe with Carbon's 3D printing technology

California 3D printer manufacturer Carbon (Carbon3D) has teamed with German sportswear giant Adidas to create a new 3D printed shoe. The companies will use Carbon's Digital Light Synthesis technique to mass-produce more than 100,000 pairs of Adidas' Futurecraft 4D shoe before 2019.

3D PHARMA PRINTING
OVERVIEW OF THE FIELD

IMPORTANT TRENDS IN PHARMA

- Time to market -> maximize benefits from patent life
- Personalization -> smaller batch sizes
- Focus on continuous manufacturing, Quality by design

WHY 3D PHARMA PRINTING?
USP'S OF 3D PRINTING

- Personalization
- Small batches
- Unique functionalities: release profile, poly pill, shape
- Distributed local manufacturing

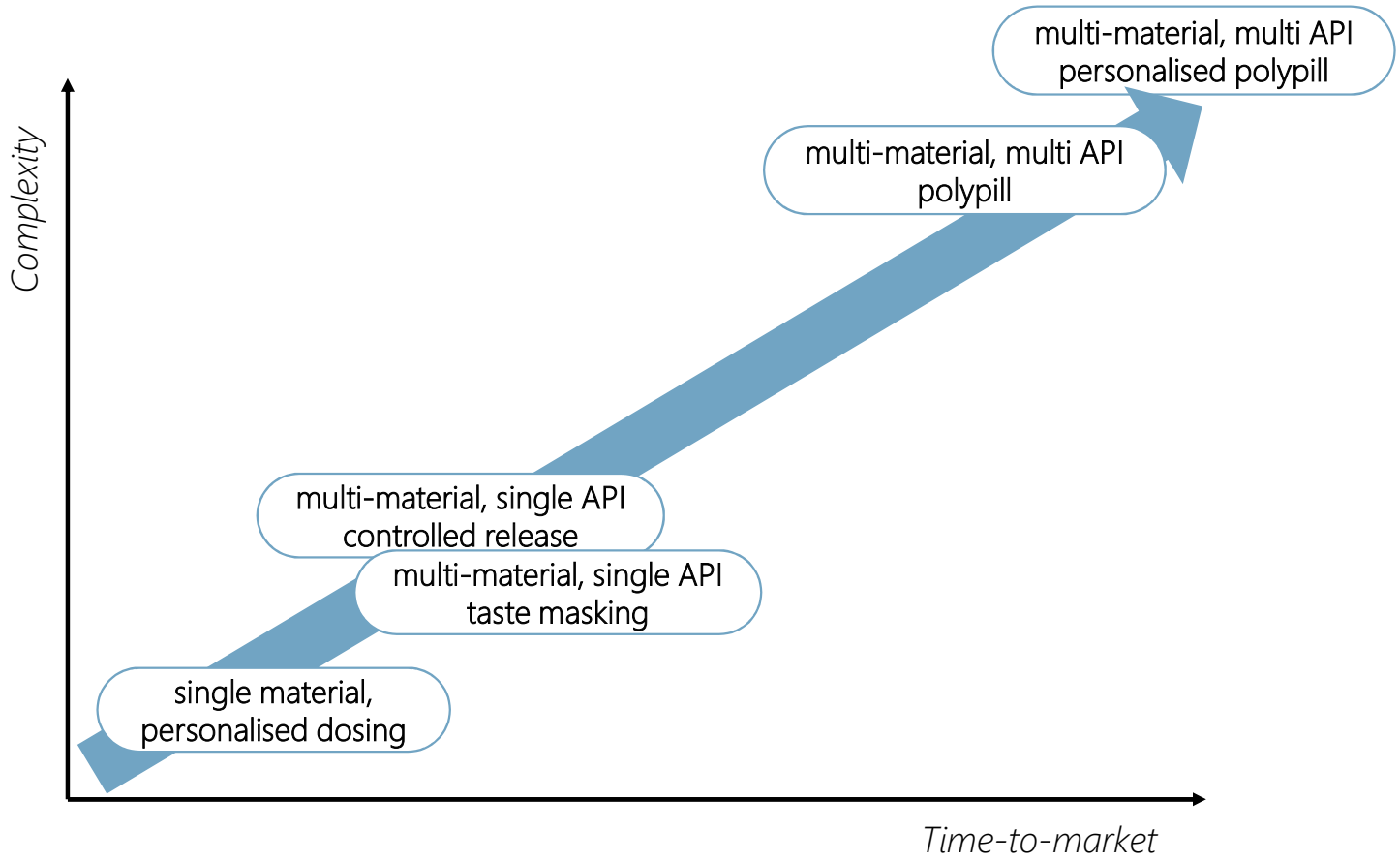
3D PHARMA PRINTING
SOCIETAL IMPACT

Contribution to:

- Better Health
- More effective medication
- Better patient comfort

3D PHARMA PRINTING @ TNO

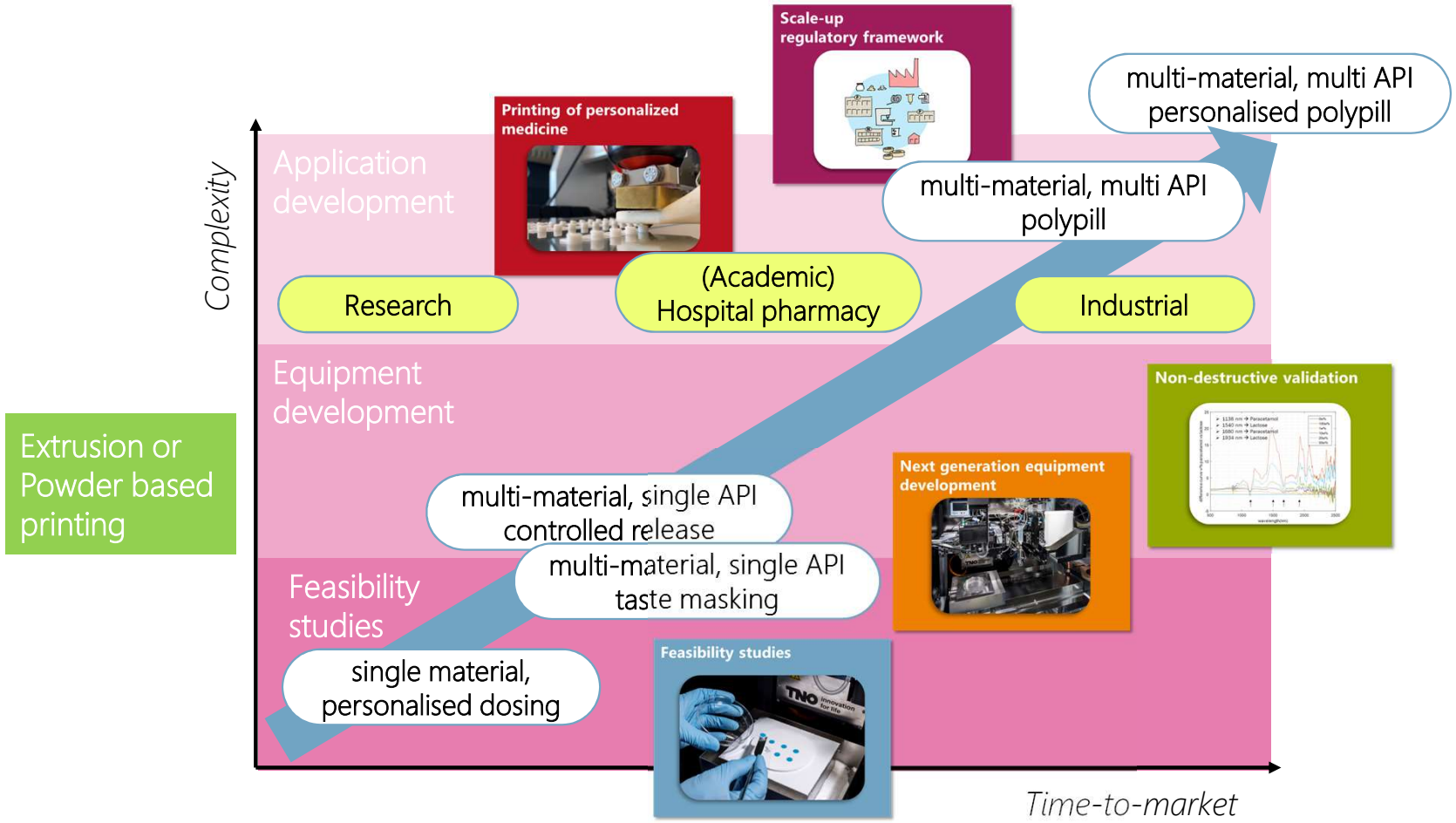
ROADMAP



TNO innovation for life

3D PHARMA PRINTING @ TNO

ROADMAP



TNO innovation for life

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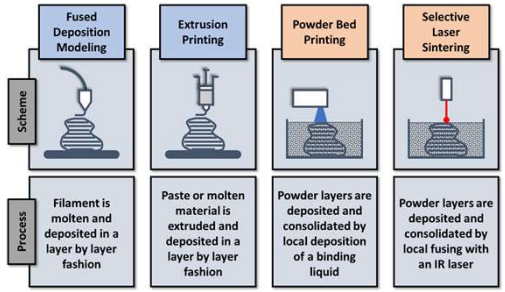
IN-HOUSE DEVELOPED TECHNOLOGY PLATFORMS



Extrusion printing en fused deposition modelling

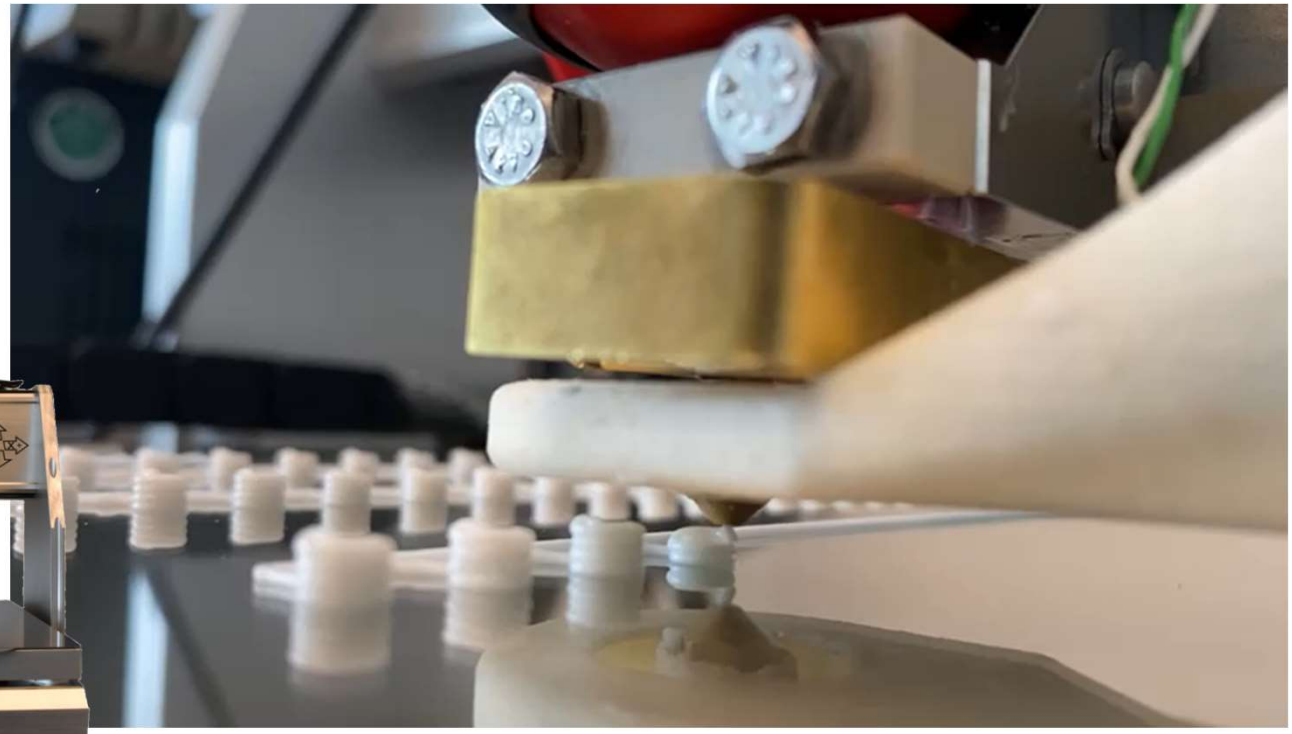
High speed extrusion printing with multiple materials

Up-scaling Technologies

Powder bed printing and Selective laser sintering (separate or combined)

3D PHARMA PRINTING @ TNO

FEASIBILITY STUDIES – EXTRUSION PRINTING



Extrusion Printing

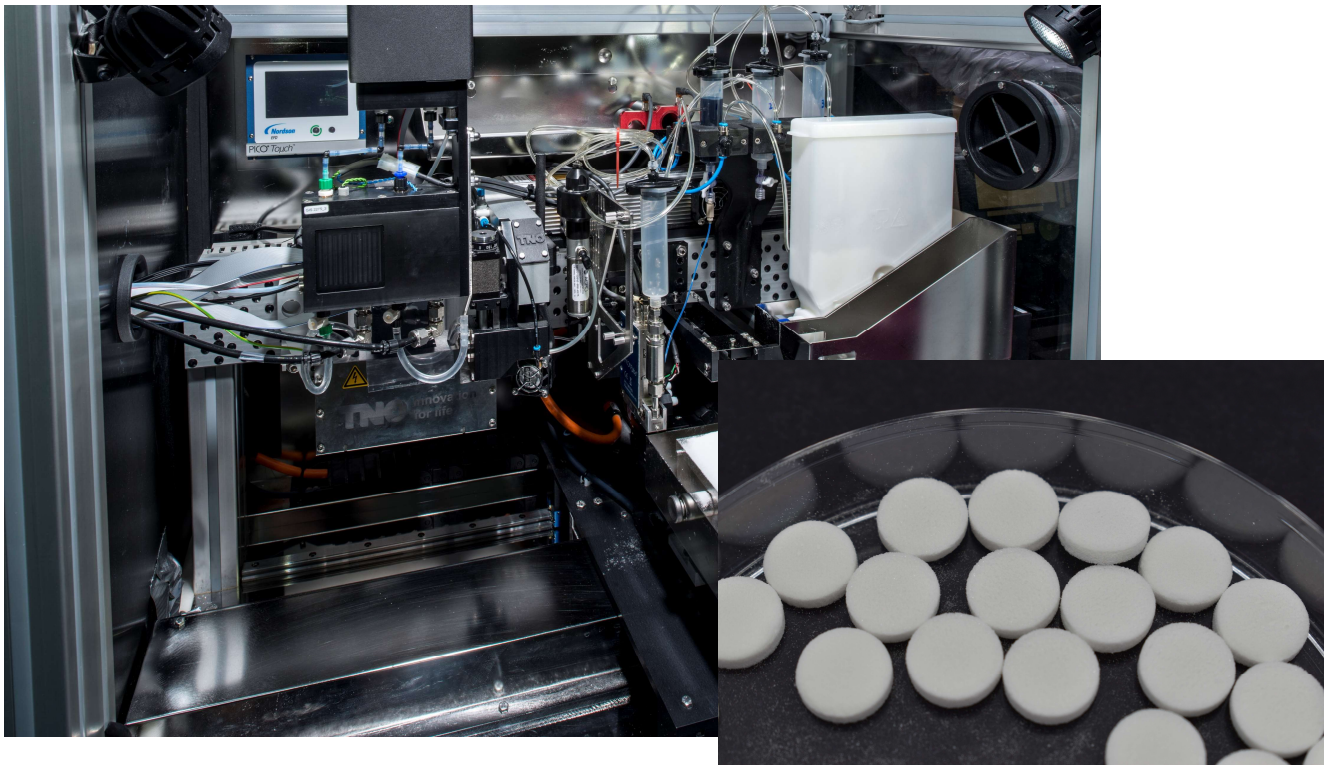
Scheme

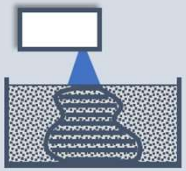
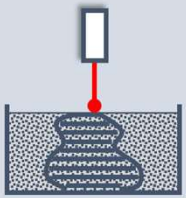
Process

Paste or molten material is extruded and deposited in a layer by layer fashion

3D PHARMA PRINTING @ TNO
FEASIBILITY STUDIES – PBP/SLS

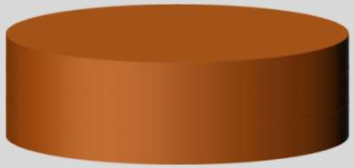
- Combination Binder Jetting and Selective Laser Sintering



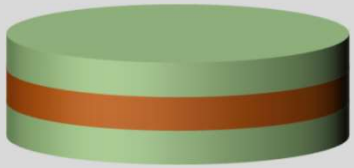
	Powder Bed Printing	Selective Laser Sintering
Scheme		
Process	Powder layers are deposited and consolidated by local deposition of a binding liquid	Powder layers are deposited and consolidated by local fusing with an IR laser

LAYERED TABLET CONCEPT

reference



layered



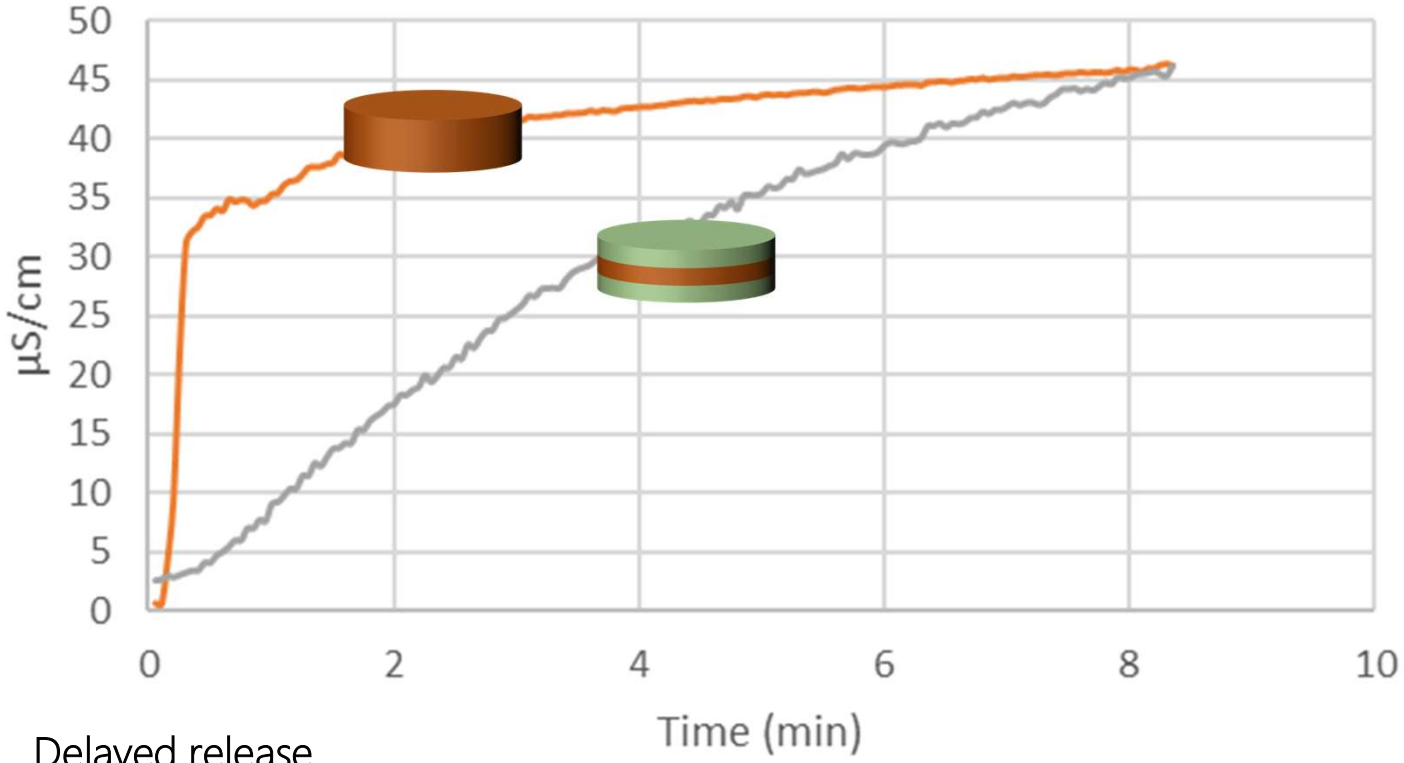
Layer Types

Differences created through printing liquid:

Slow dissolving

Fast dissolving

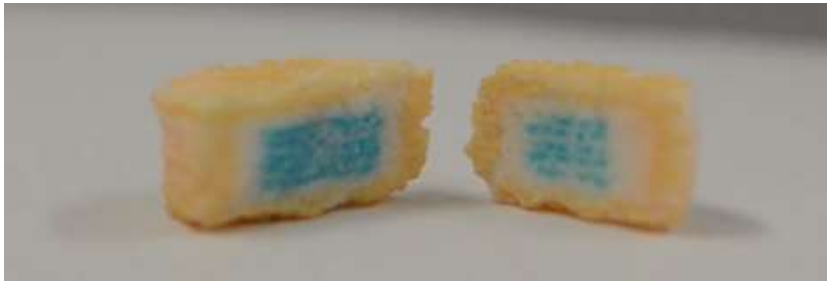
API RELEASE



Delayed release

Model API (ionic species) release was monitored by conductivity measurements.

SEGMENTED TABLET CONCEPT



3-tone variation

Complex geometry

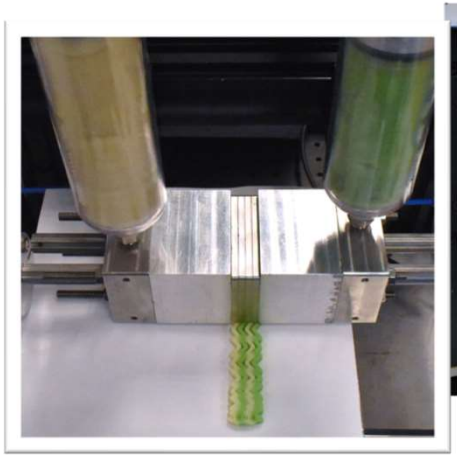
Fast dissolving + API 1

Slow dissolving

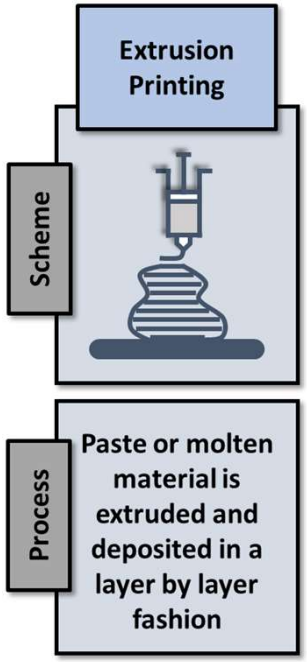
Fast dissolving + API 2

COMPLEX RELEASE PROFILES

3D PHARMA PRINTING @ TNO
NEXT GENERATION EQUIPMENT DEVELOPMENT



- Our multi-nozzle printhead platform allows printing with multiple materials simultaneously.
- This experimental printhead platform can be used to explore the potential of novel extrusion concepts for continuous and large-scale production.

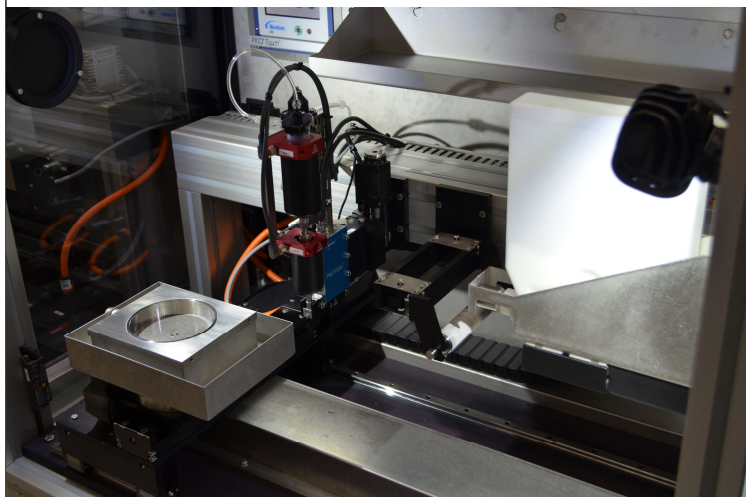


3D Pharma printing @ TNO, 2022

PROJECT EXAMPLE

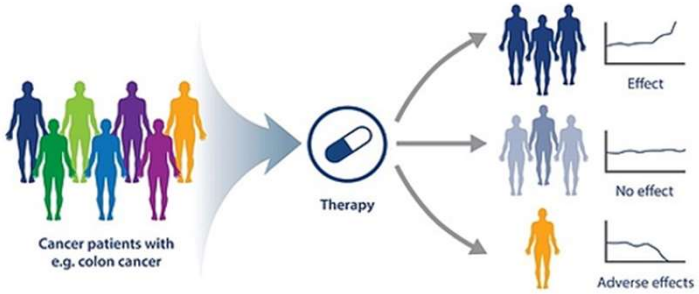
MERCK – PHARMA R&D SETUP

- TNObuilt a dedicated powderbed-printing setup for Merck so they could research their proprietary powder formulas and APIs.
- Using powderbed printing, tablets for preclinical development and screening of APIs can be made more efficiently and with higher accuracy.
- Merck is using the setup to determine their own roadmap for 3D pharma printing

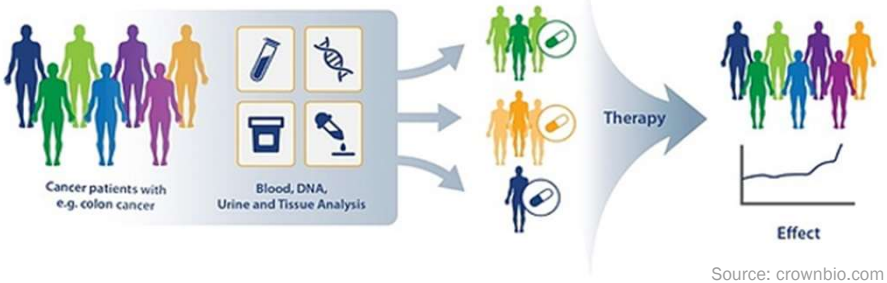


3D PHARMA PRINTING
PRINTING OF PERSONALIZED MEDICINE

Current Medicine
One treatment fits all



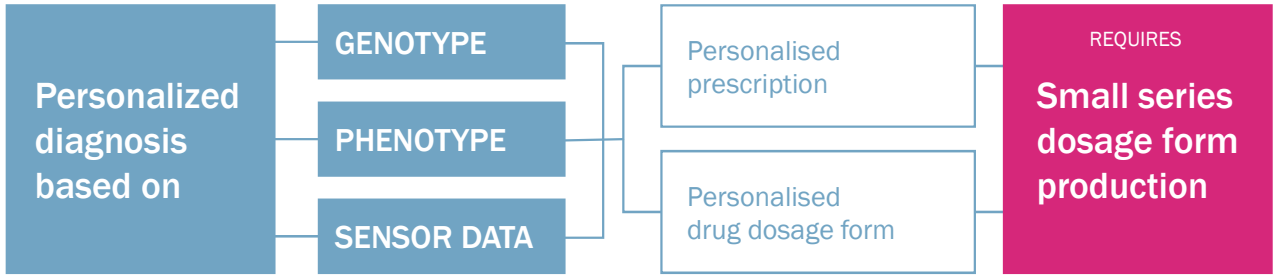
Future Medicine
More personalized diagnostics



Source: crownbio.com

FROM:
ONE SIZE FITS ALL

TO:
TAILORED APPROACH

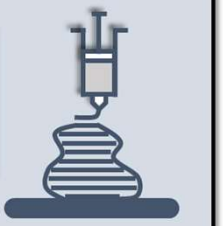


3D PHARMA PRINTING @ TNO

PRINTING OF PERSONALIZED MEDICINE

Extrusion Printing

Scheme

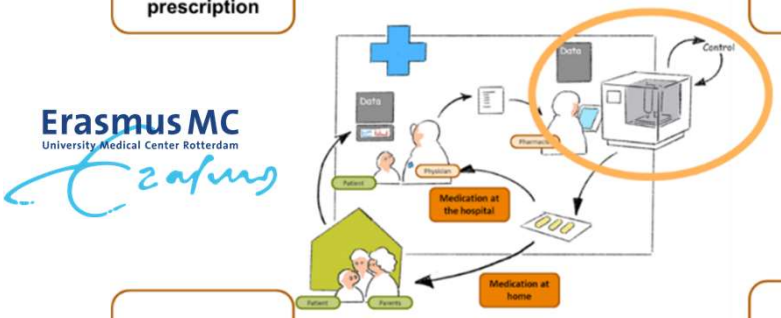


Process

Paste or molten material is extruded and deposited in a layer by layer fashion

Personalized diagnosis and prescription

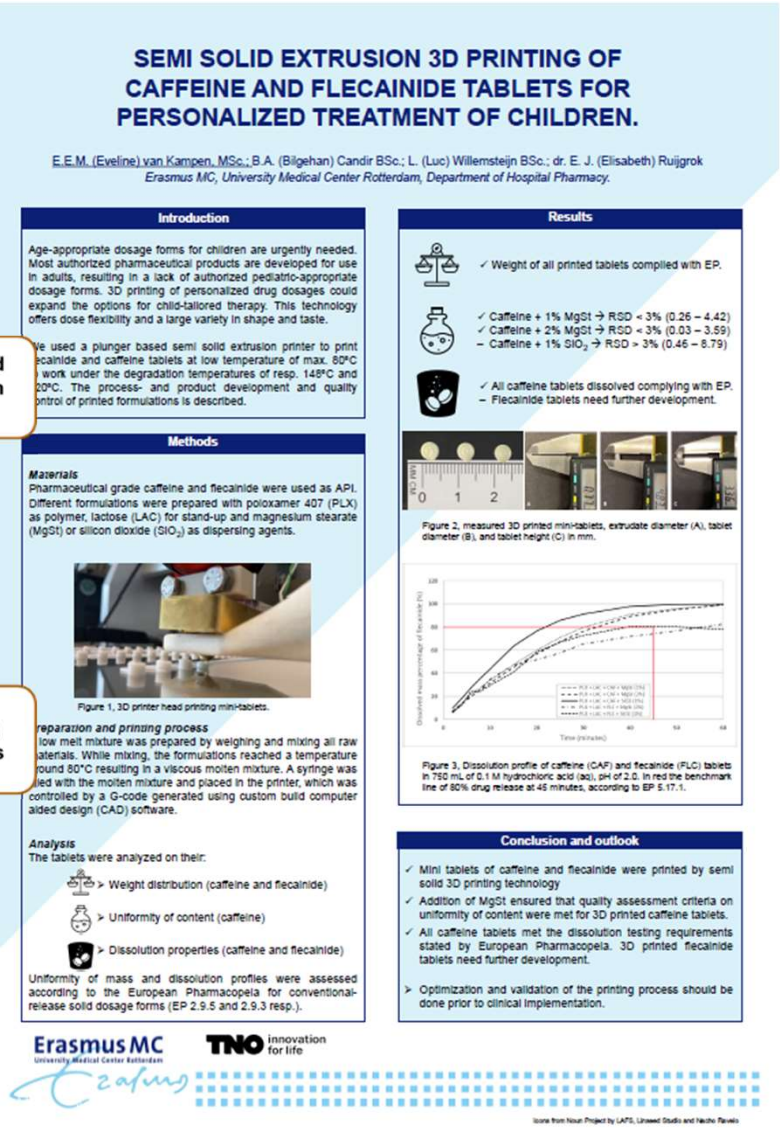
Personalized dosage form production



Application and acceptance

Distribution and logistics

Allow for safe and affordable production
of tailor made medication for individual patients
by developing technological solutions
for automated production in the hospital pharmacy



SEMI SOLID EXTRUSION 3D PRINTING OF CAFFEINE AND FLECAINIDE TABLETS FOR PERSONALIZED TREATMENT OF CHILDREN.

E.E.M. (Eveline) van Kampen, MSc.; B.A. (Bilgehan) Candir BSc.; L. (Luc) Willemsteijn BSc.; dr. E. J. (Elisabeth) Ruijgrok
Erasmus MC, University Medical Center Rotterdam, Department of Hospital Pharmacy.

Introduction

Age-appropriate dosage forms for children are urgently needed. Most authorized pharmaceutical products are developed for use in adults, resulting in a lack of authorized pediatric-appropriate dosage forms. 3D printing of personalized drug dosages could expand the options for child-tailored therapy. This technology offers dose flexibility and a large variety in shape and taste.

We used a plunger based semi solid extrusion printer to print flecainide and caffeine tablets at low temperature of max. 60°C to work under the degradation temperatures of resp. 148°C and 220°C. The process- and product development and quality control of printed formulations is described.

Methods

Materials
Pharmaceutical grade caffeine and flecainide were used as API. Different formulations were prepared with poloxamer 407 (PLX) as polymer, lactose (LAC) for stand-up and magnesium stearate (MgSt) or silicon dioxide (SiO_2) as dispersing agents.

Figure 1, 3D printer head printing mini-tablets.

Preparation and printing process
A low melt mixture was prepared by weighing and mixing all raw materials. While mixing, the formulations reached a temperature around 80°C resulting in a viscous molten mixture. A syringe was filled with the molten mixture and placed in the printer, which was controlled by a G-code generated using custom build computer aided design (CAD) software.

Analysis
The tablets were analyzed on their:

- Weight distribution (caffeine and flecainide)
- Uniformity of content (caffeine)
- Dissolution properties (caffeine and flecainide)

Uniformity of mass and dissolution profiles were assessed according to the European Pharmacopeia for conventional-release solid dosage forms (EP 2.9.5 and 2.9.3 resp.).

Results

- ✓ Weight of all printed tablets complied with EP.
- ✓ Caffeine + 1% MgSt → RSD < 3% (0.26 – 4.42)
- ✓ Caffeine + 2% MgSt → RSD < 3% (0.03 – 3.59)
- – Caffeine + 1% SiO_2 → RSD > 3% (0.46 – 8.79)
- ✓ All caffeine tablets dissolved complying with EP.
- – Flecainide tablets need further development.

Figure 2, measured 3D printed mini-tablets, extrudate diameter (A), tablet diameter (B), and tablet height (C) in mm.

Figure 3, Dissolution profile of caffeine (CAF) and flecainide (FLC) tablets in 750 mL of 0.1 M hydrochloric acid (aq), pH of 2.0. In red the benchmark line of 80% drug release at 45 minutes, according to EP 5.17.1.

Conclusion and outlook

- ✓ Mini tablets of caffeine and flecainide were printed by semi solid 3D printing technology
- ✓ Addition of MgSt ensured that quality assessment criteria on uniformity of content were met for 3D printed caffeine tablets.
- ✓ All caffeine tablets met the dissolution testing requirements stated by European Pharmacopela. 3D printed flecainide tablets need further development.
- ➢ Optimization and validation of the printing process should be done prior to clinical implementation.

Erasmus MC University Medical Center Rotterdam
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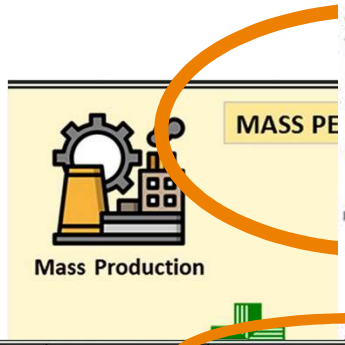
Icons from Noun Project by LAFS, Linawati Studio and Nacho Ranedo

3D PHARMA PRINTING
ROADS TO MARKET



Contents lists available at ScienceDirect

Exploratory Research in Clinical and Social Pharmacy

journal homepage: www.elsevier.com/locate/rcsop

Scenarios for 3D printing of personalized medicines - A case study

Kaae [a], Marie Louise De Bruin [c,d], Natalja Genina [a],
ert [b], Sofia Kälvemark Sporrong [a,e,*]

and the Environment (RIVM), Bilthoven, the Netherlands
acy, University of Copenhagen, Copenhagen, Denmark
Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

Scenario / HTA	Industry	Compounding facility	Large hospital pharmacy	Community pharmacy or small hospital pharmacy	Home
Regulatory					
Economic					
Ethical					
Organizational					

Serious challenge | Moderate challenge | Minimal challenge

Disaster Areas

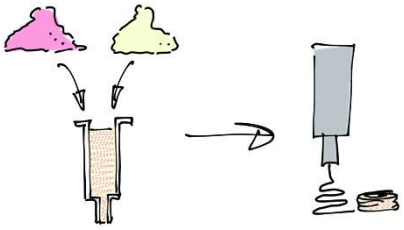
d clinical applications.
ivery Reviews (2021)

Source: Scenarios for 3D printing of personalized medicines - A case study; Netta Beer et al. 2021

3D PHARMA PRINTING

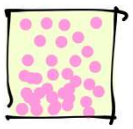
SMALL SERIES OR COMPLICATED TABLETS - HOW TO VALIDATE QUALITY?

- When producing ever smaller series of tablets of ever more complicated tablets (f.i. polypill)
  -> Destructive testing will be no longer a valid solution.

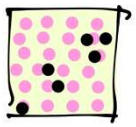


Which API?
API dose?

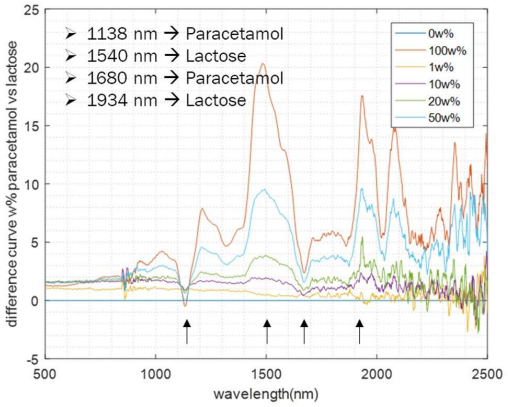
API dose = Tablet weight x API % in bulk



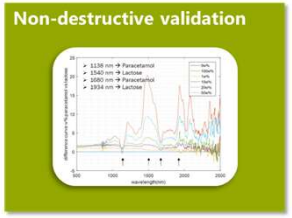
If: No inhomogeneity

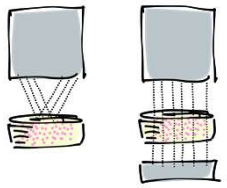


If: No API degradation

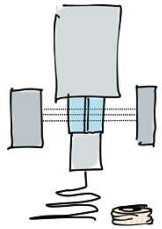


Spectral analysis

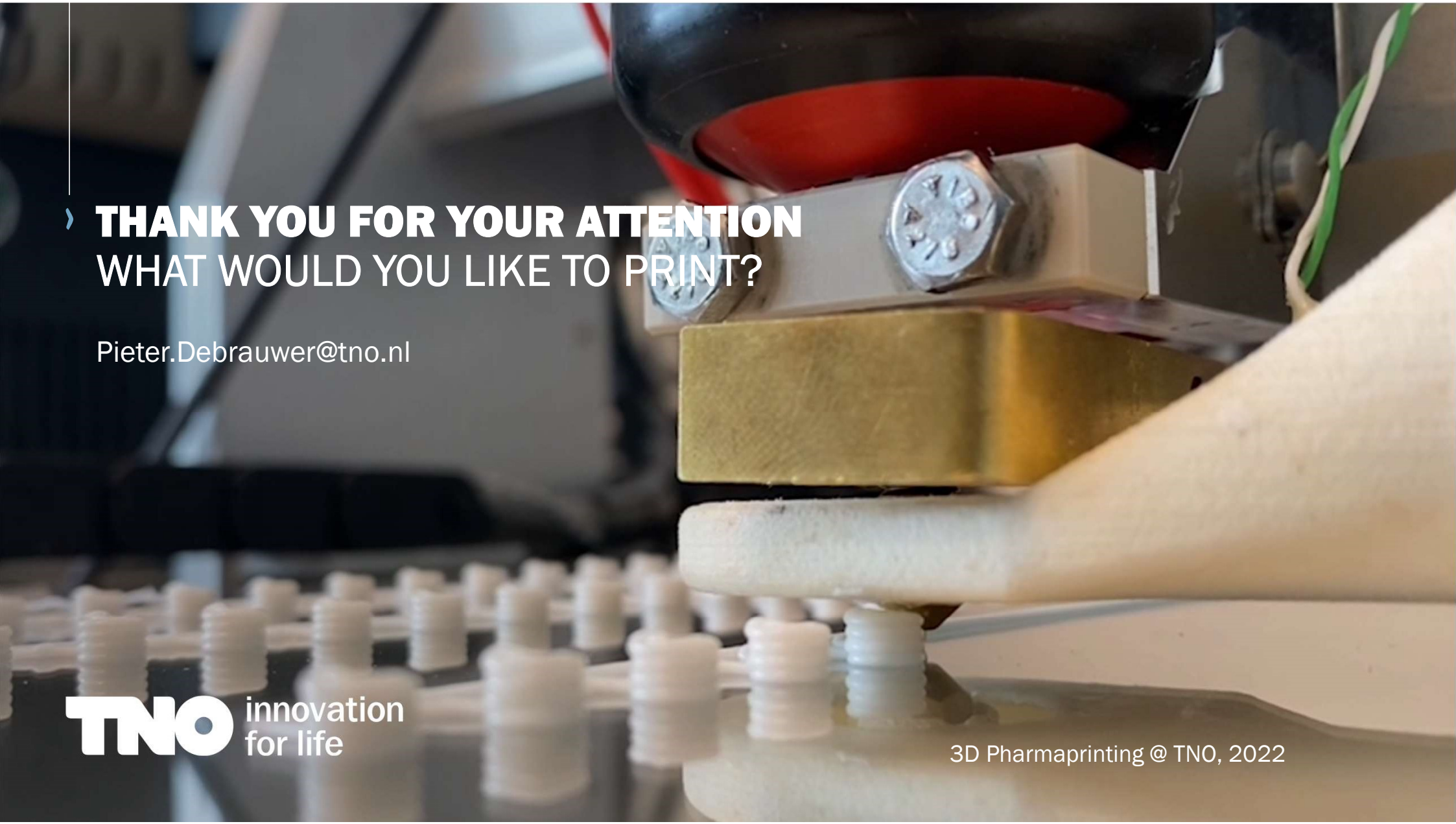




Look at tablet



Look at filament



THANK YOU FOR YOUR ATTENTION
WHAT WOULD YOU LIKE TO PRINT?

Pieter.Debrauwer@tno.nl

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