Leids Universitair Medisch Centrum

GMP: more than just a 3 letter word

It is a state of mind: from theory to practice

Kirsten Schimmel, PharmD, PhD
Hospital pharmacist
Leiden Academic Medical Centre
The Netherlands

MARCH 2021

Conflicts of interest

Relevant Financial Relationship

None

Off-Label Investigational Uses

None

Questions: Yes or No

1 Cross contamination: is no issue in individual preparations due to the small scale
2 ATMP production falls under the general GMP
3 QP (qualified person) is mandatory for stock preparations in a pharmacy

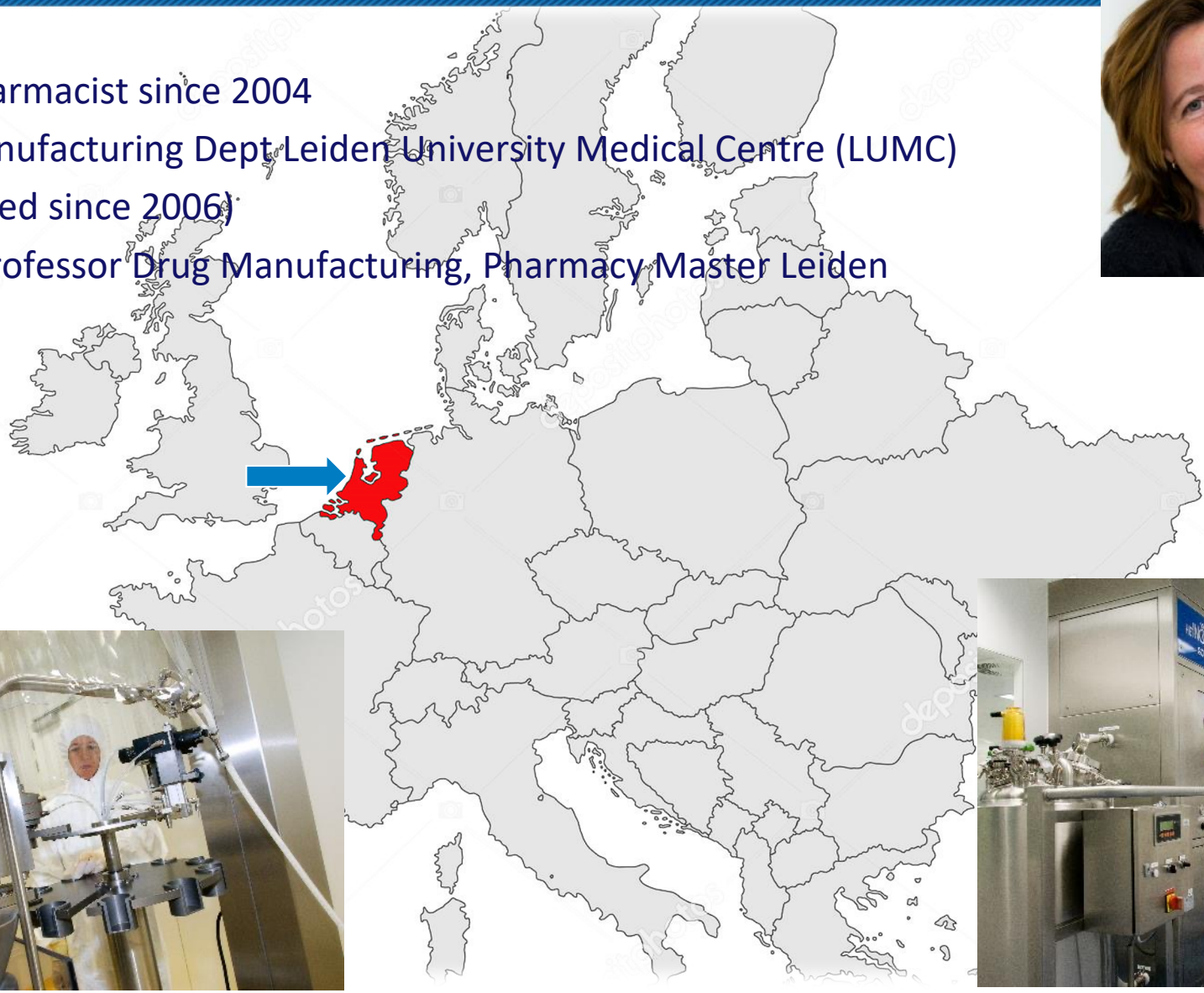
Let me introduce myself

Hospital Pharmacist since 2004

Head of Manufacturing Dept Leiden University Medical Centre (LUMC)

(GMP licensed since 2006)

Associate Professor Drug Manufacturing, Pharmacy Master Leiden



Why Rules?

1930's

1960's

Cases we have to deal with in real life:

1. Cross contamination
2. From extemporaneous preparation (sterile, non sterile) to large scale
3. Reconstitution: aseptic handling
   - from nurse bench to pharmacy, EU Resolution CM/Res(2016)2
4. Radiopharmaceuticals
   - kits to synthesis, GCP
5. Cell based products: GMP ATMP
   - what does individual pharmacist needs to know
6. Innovations: 3D printer, personalized therapeutics

1. Cross contamination

Hospital Pharmacy

Industry

Picture: https://en.wikipedia.org/wiki/Drug_packaging

What's in the GMP?

Chapter 3: Premises and equipment: 3.6: Cross-contamination:

- Measures should be in line with the risks: use Quality Risk Management
- Refers to Chapter 5, GMP for ATMP (former Annex 2), Annex 3, 4, 5, 6

- Chapter 5: Production: section 17-21
  - Risk assessment
    - avoid as much as possible, or justify
    - Design of premises-equipment
    - Toxicological assessment including potency and toxicological evaluation
  - Outcome of Risk Assessment: Technical & Organizational Measures

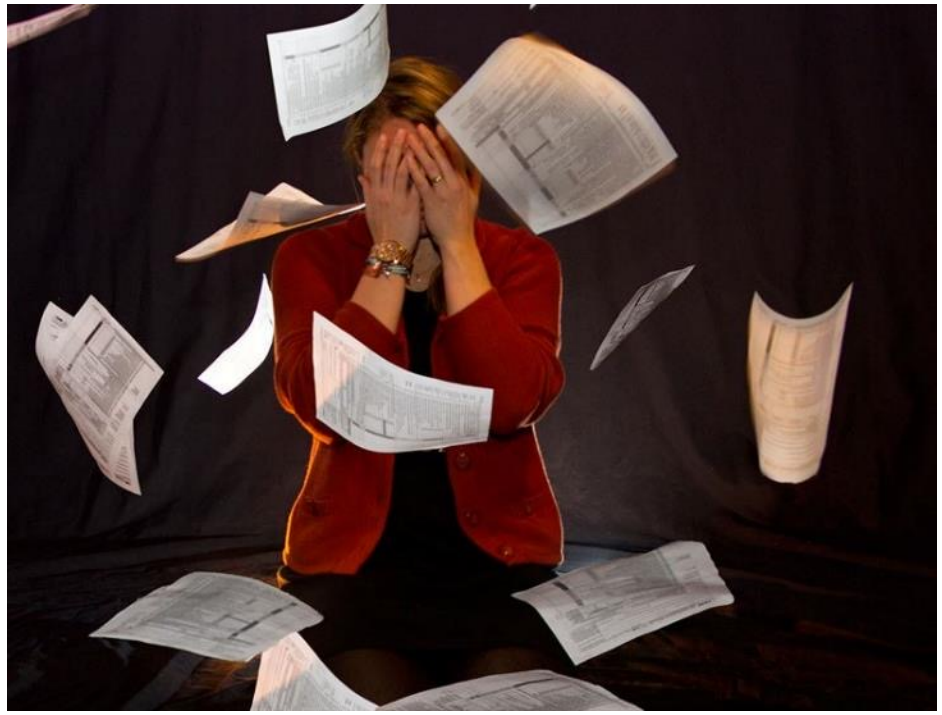
- GMP for ATMP
- Annex 3-6: special attention to prevent cross contamination
  - Nature of product (radioactive, immunological)
  - Size of production (veterinary)
  - Use: gas containers

PDE: how to deal with them

Permitted daily exposure: involves toxicity data in cross contamination

Requires extensive literature research per substance

Hospital pharmacy: 150 different products with approximately 100 different API’s



Plan of Action

RAE: Risk Assessment and Evaluation

Risk: Cross Contamination leading to toxic effects

Assessment

- Identify different steps
- Measurements already taken

Evaluation

- Can risk be mitigated and controlled?
- Are measures taken feasible?
- Are measures effective

Example of risk assessment: Cross contamination

Step	Severity	Probability	Detectability	Measurements taken	Final Risk score
Weighing: contamination of raw materials	H	L	M	Suction Cabinet 1 open vessel at a time Cleaning	L
Premises: leftovers contaminate next production	M	L	H	Cleaning and line clearance	L
Equipment	H	M	M	Cleaning validation Use of disposables	L
Personnel: can transfer contamination to next production	H	M	M	SOP Training Protective clothing	L
Toxic effects: If not taken into account, risk of contamination cannot be assessed	M	M	H	Worst case approach Compare with cleaning validation limits	L
Etc etc etc					

Case 2: Individual preparation

Case:

Tom, 3 months old suffering from a heart condition needs anticoagulant therapy after surgery. Doctor prescribes: 0.6 mg fenprocoumon, to be started this afternoon

Available in the pharmacy:

- 3mg fenprocoumon tablets
- No other vitamin K antagonist
- Low molecular weight heparin
- Heparin

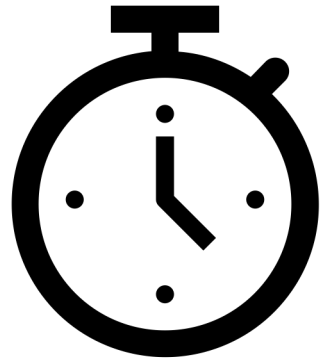
What would you do?

Extemporeaneous Preparations
Old school Personalized therapy

Suspension based on tablets

Assessment of:

- Pharmacotherapy
- Technical aspects
- Skills of personnel
- Availability of materials



few hours

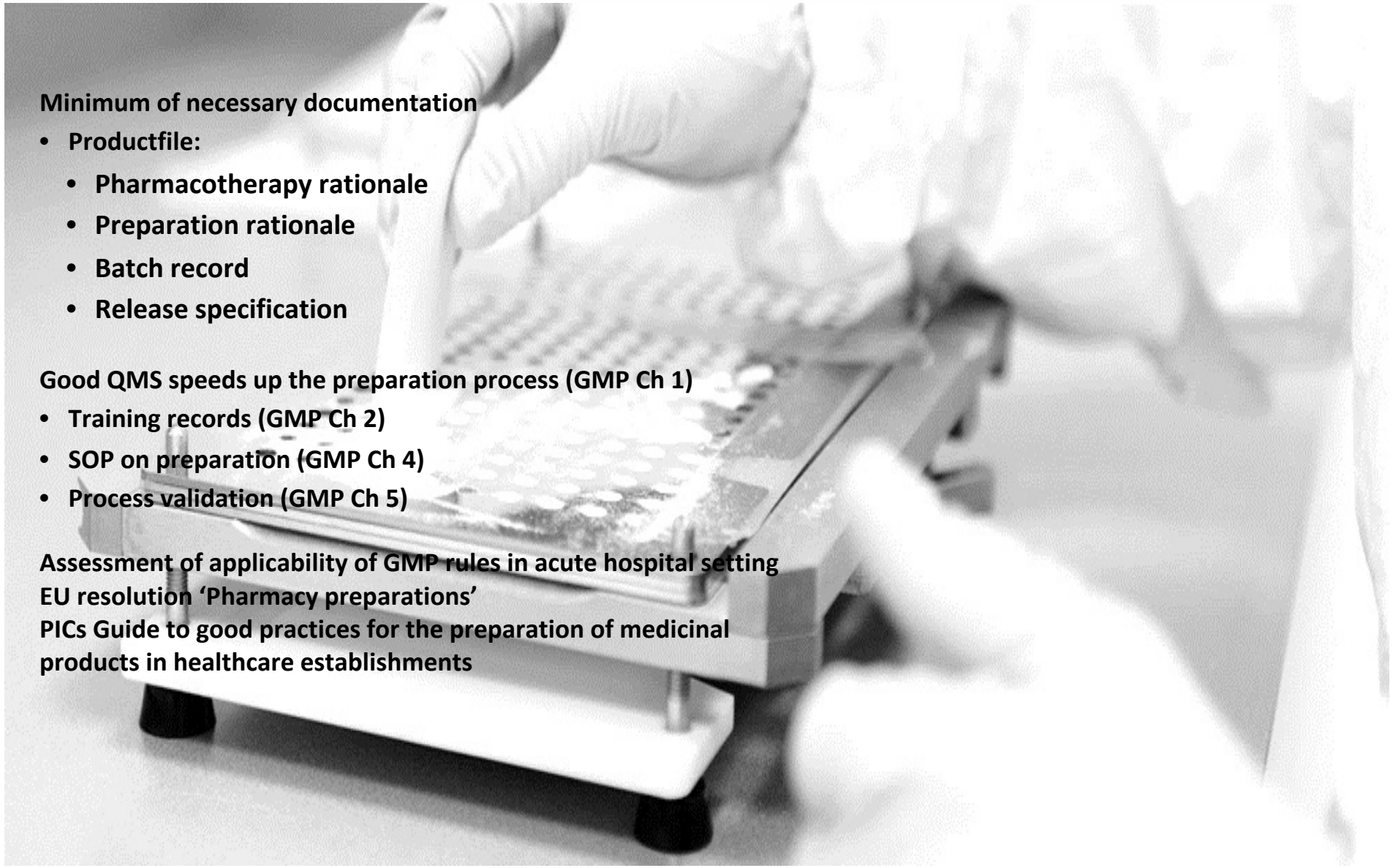
Which rules do apply?

National regulations

However: which GMP principles are involved?

Which other documentation might help?

Extemporaneous preparation



Minimum of necessary documentation

- **Productfile:**
  - **Pharmacotherapy rationale**
  - **Preparation rationale**
  - **Batch record**
  - **Release specification**

Good QMS speeds up the preparation process (GMP Ch 1)

- **Training records (GMP Ch 2)**
- **SOP on preparation (GMP Ch 4)**
- **Process validation (GMP Ch 5)**

Assessment of applicability of GMP rules in acute hospital setting
EU resolution 'Pharmacy preparations'
PICs Guide to good practices for the preparation of medicinal products in healthcare establishments

Upscaling

Suspension was successful, a new cardiac surgeon joins the hospital performing more operations leading to an increased request for the suspension

Decision:

Transfer of the preparation from individual base to stock preparation

Remains a pharmacy preparation (no marketing approval)

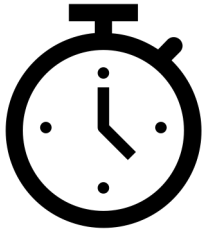
What changes?

Scale: risk assessment

Stock preparation

Quality control: analytical testing

Validation of analytical method



Several weeks

Full GMP?

Not necessary however:

process will heavily rely on information in GMP

Case 3: Aseptic handling: from nurse bench to pharmacy cleanroom

Available rules

EU resolution:

CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use.

GMP Annex 1:

Manufacture of sterile medicinal products

Rules involved

EU resolution:

CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use.

For clinical wards

GMP Annex 1:

Manufacture of sterile medicinal products

aseptic manufacturing ≠ reconstitution

However: in both guidances useful information

Aseptic manufacturing ≠ aseptic handling

Aseptic manufacturing: The process used for products that cannot be sterilised in their final container, i.e. cannot be terminally sterilised .

Aseptic processing is called aseptic preparation in Annex 1

Aseptic handling: The process to enable sterile products to be made ready to administer, using closed systems

Closed procedure: A procedure whereby a sterile pharmaceutical product is prepared by transferring sterile ingredients or solutions to a pre-sterilised container, either directly or using a sterile transfer device, without exposing the solution to the external environment

What can be used from the regulations?

EU resolution

- Designated person with overall responsibility for reconstitution
- Risk assessment: on the ward or in the pharmacy

Annex 1

- Guidances for equipment requirements
- Limits for viable and non-viable particles

Case 4 Radiopharmacy: from reconstitution to synthesis

GMP Annex 3: Radiopharmaceuticals

Note i. Preparation of radiopharmaceuticals in radiopharmacies (hospitals or certain pharmacies), using Generators and Kits with a marketing authorisation or a national licence, is not covered by this guideline, unless covered by national requirement.

Not applicable for kits

Note ii. According to radiation protection regulations it should be ensured that any medical exposure is under the clinical responsibility of a practitioner. In diagnostic and therapeutic nuclear medicine practices a medical physics expert shall be available.

Note iii. This annex is also applicable to radiopharmaceuticals used in clinical trials.

National regulations for reconstitution

- Aseptic handling
- Similarities with handling cytotoxic drugs
- Radiosafety requirements

However: what to do in case of synthesis?

EP:

- 5.19: Extemporeaneous preparation of radiopharmaceuticals
  - Includes synthesis
  - Drawing individual doses out of multidose vial is not preparation but clinical practise

Producing of the starting materials:

- Part II of GMP

Radioactive:

- Annex 3: Radiopharmaceuticals

Clinical Trials:

- Annex 13: Manufacture of Investigational Medicinal Products

Clinical Trial Regulation EU No 536/2014

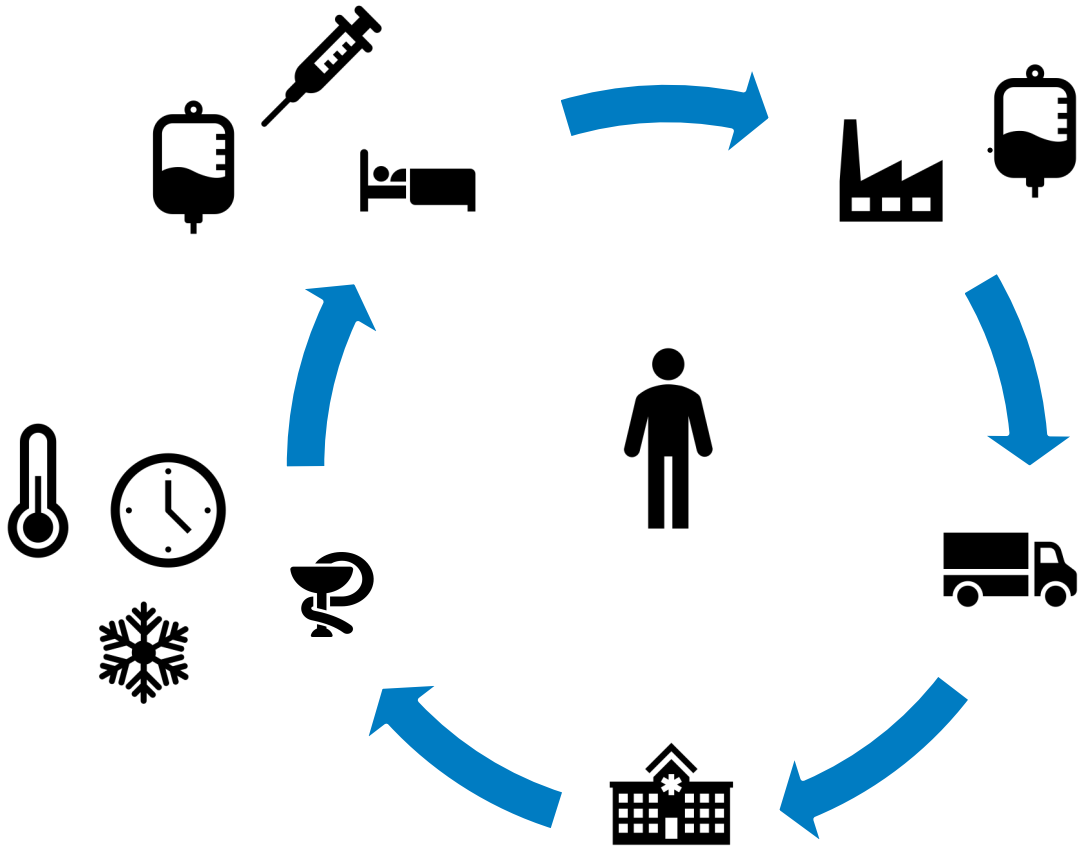
- Not applicable yet
- No GMP license for diagnostic radiopharmaceuticals if carried out in hospitals

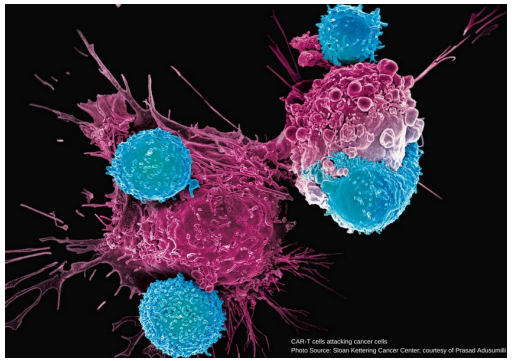
Case 5: Innovative products: ATMP

Pharmacy involvement:

- production in house or ‘ only’ receive and distribute to patient?

'separate’ GMP: Volume 4





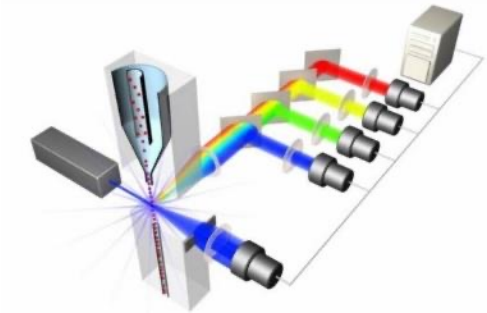
Car-T cells

Facilities ATMPs: production in house

- Dedicated cleanrooms (class A in B)

- Specific equipment

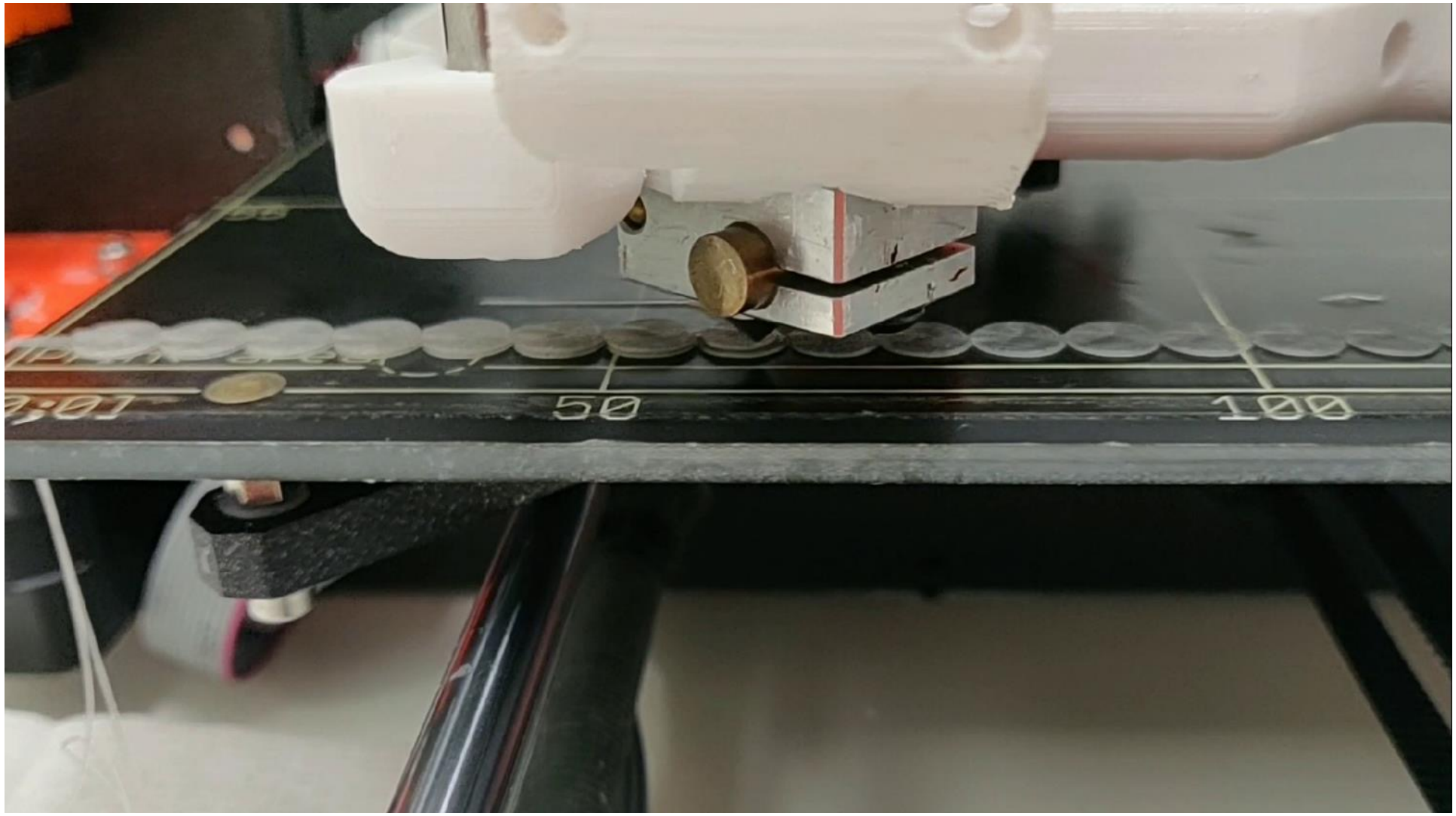
- CO_2-incubators for culture



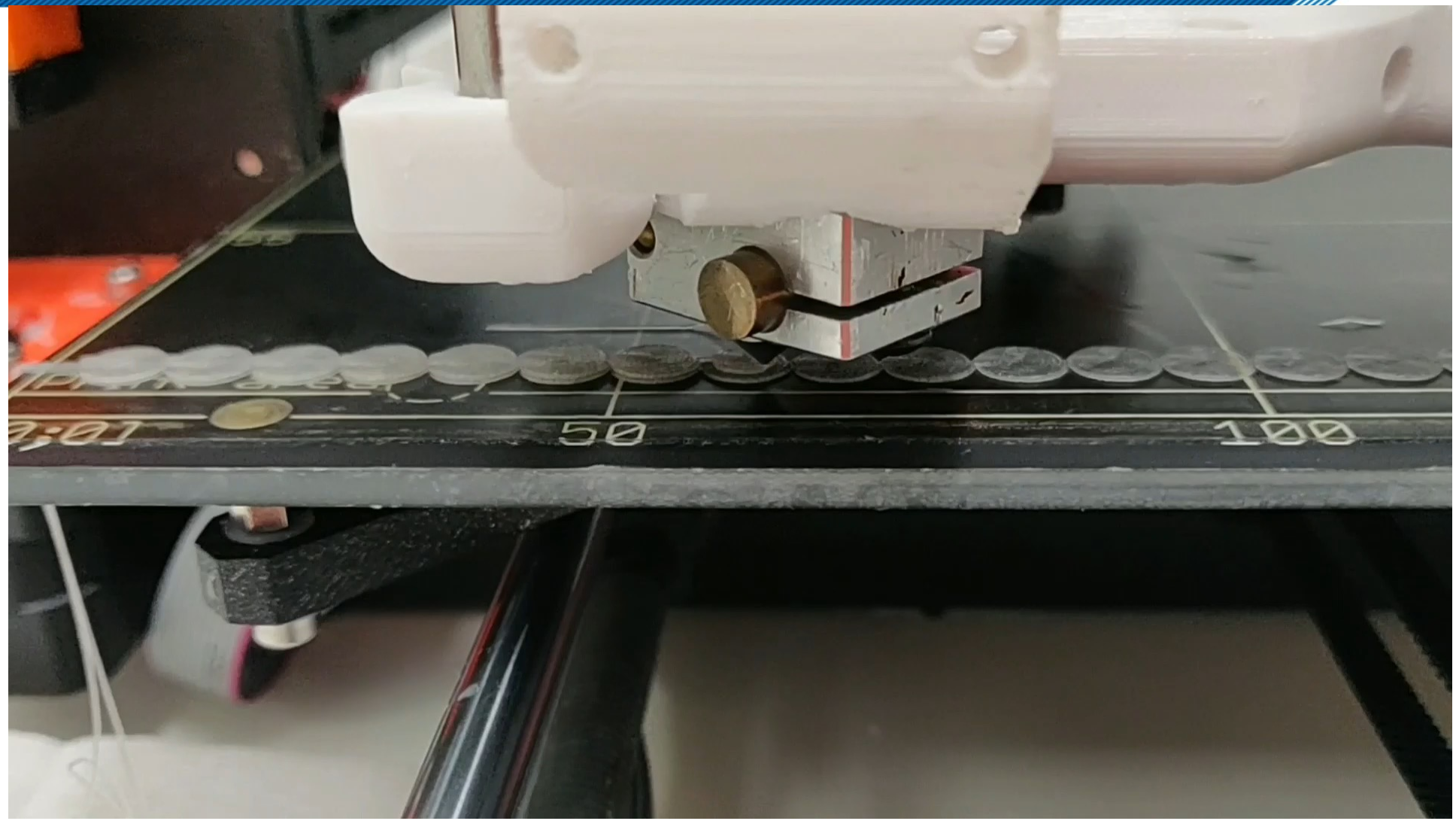
- QC equipment, e.g. FACS

- Cryopreservation

Case 6: Innovative techniques in pharmacy: 3D printer



Case 6: Innovative techniques in pharmacy: 3D printer



How to introduce a new technique?

…by applying the old principles

‘Quality by design’ meets GMP

- Risk assessment of the process
- Identify critical process parameters
- Materials
- Equipment
- Manufacturing process
- Analytical activities

- Do not overestimate the pharmaceutical knowledge of your partner

Example of regulation in Hospital Pharmacy: The Dutch situation: GMP Hospital pharmacy

Old situation: for every chapter own ‘hospital’ version

- Revision: per chapter 1 or 2 situations different in hospital pharmacy:
  - No marketing approval
  - QP not necessary, however QA performs almost same tasks
- However: 4 specific hospital chapters:
  - Appraisal of preparation request and design quality
  - Individual preparations
  - Aseptic handling
  - Handling high risk substances and preparations

Conclusion: challenges in pharmacy preparations: GMP can help

Different rules to be applied

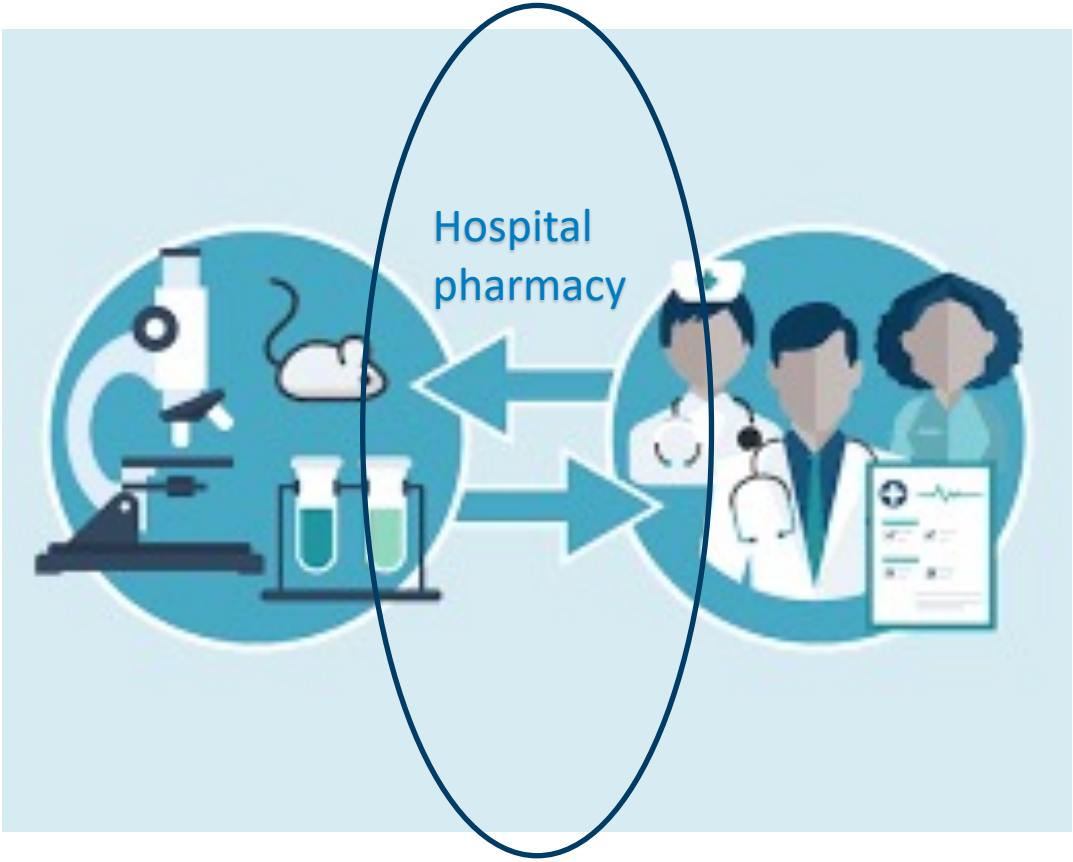
Heterogeneity in products

High demands for:

Skills: education/training

Availability of supplies

Quality of supplies



Take home messages

- GMP principles are always useful when making pharmacy preparations
- Pharmacy preparations require an individual and risk based approach on how and when to apply which rules
- Patient care may require a deviation from the rules, however this should be risk based