

Martini Ziekenhuis Groningen

# Extractables and leachables from syringes

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# Content presentation

- Legislation and regulations
  - GMP/GMP-z
  - Geneesmiddelenwet (Dutch Medicines Act)
- Production in Martini Hospital
- Qualification of primary packaging material
- Extractables and leachables
- Practical example



# Legislation and regulations

- Hospital pharmacies vs compounding pharmacies vs pharmaceutical industry
- Different types of production – which regulation applicable?

| Scale                          | Quality level | File                           | Testing authority |
|--------------------------------|---------------|--------------------------------|-------------------|
| Magistral preparations         | GMP-z         | According to SmPC              | IGJ               |
| Small-scale preparations       | GMP-z         | Product specifications (short) | IGJ               |
| Officinal (stock) preparations | GMP           | Product specifications         | IGJ               |
| Marketing authorization        | GMP           | Registration file              | CBG               |

SmPC – Summary of Product Characteristics

IGJ – Dutch Health Care Inspectorate

CBG – Dutch Medicines Evaluation Board



# GMP-z production in hospital pharmacies

- **Preparations for individual patients (magistral)**
  - Prescription required in advance
  - For example: chemotherapy, oral solutions for children, antibiotic infusions
  - Short shelf life, no regular analysis on final product
  - Release by (compounding) pharmacist
- **Stock preparations (in-hospital use)**
  - Limited numbers of patients per year
  - For example: ready-to-administer (RTA) syringes
  - Shelf life based on studies and part of the product specifications



# Dutch Medicines Act



Health and Youth Care Inspectorate  
Ministry of Health, Welfare and Sport

## Medicines without marketing authorization

The Dutch Medicines Act (Geneesmiddelenwet) **prohibits the sale, distribution or supply of any pharmaceutical product** (medicine) which has not been registered and granted a **marketing authorization in the Netherlands**.

However, the Act also provides for a number of **exceptions in specific circumstances**, which are described in Article 40 of the Act.

- Compassionate use
- Supply of medicines to a Doctor's Declaration
- **Collegial delivery of pharmacy compounded medicinal products**

**-> Additional requirement set by the Inspectorate**



# GMP production in hospital pharmacies

- **Stock preparations for orther (hospital) pharmacies**
  - Ready-to-administer (RTA) syringes or ready-tot-use (RTU) preparations
  - Quality control on end product
  - Release by qualified pharmacist charged with QP duties according to GMP
  - Pharmacovigilance mandatory
- **Trial medication**
  - Manufacturing and Importation Authorization (MIA)
  - Release by QP named on MIA



# Production in Martini Hospital

## Aseptic conditions



- Batch size: 300 syringes
- Shelf life: up to 90 days

## Terminally sterilized



- Batch size: 400 L
- Shelf life: up to 3 years

# Qualification of primary packaging material

- Syringes must be qualified for their intended use
  - Immediate use vs. long-term storage
- NVZA (Dutch Association of Hospital pharmacists)
  - Appendix 2; GMP-z3
- The monograph includes different tests
  - Different test solutions
  - Specified time period DWGTWTv 26



# Qualification of primary packaging material (II)

- Appearance
  - Clarity, colour and visible particles
- pH
- Weight
  - Any permeation?
- Subvisible particles
  - Must meet the requirements for parenterals



# Qualification of primary packaging material (III)

- Silicone oil
  - Syringes contain silicone oil as a lubricant
- Closure integrity
  - Internal and external influences affect your product



# Extractables and leachables

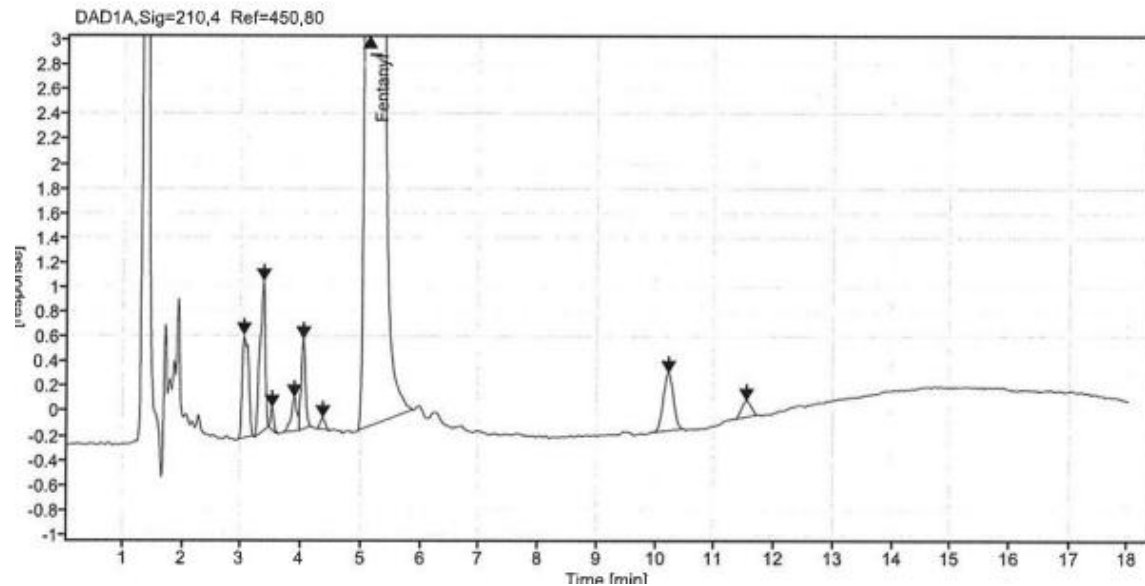
- Polymeres and additives
- Release of additives
  - Normal storage conditions: leachables
  - Research conditions: extratables
- No identification
- Challenging test



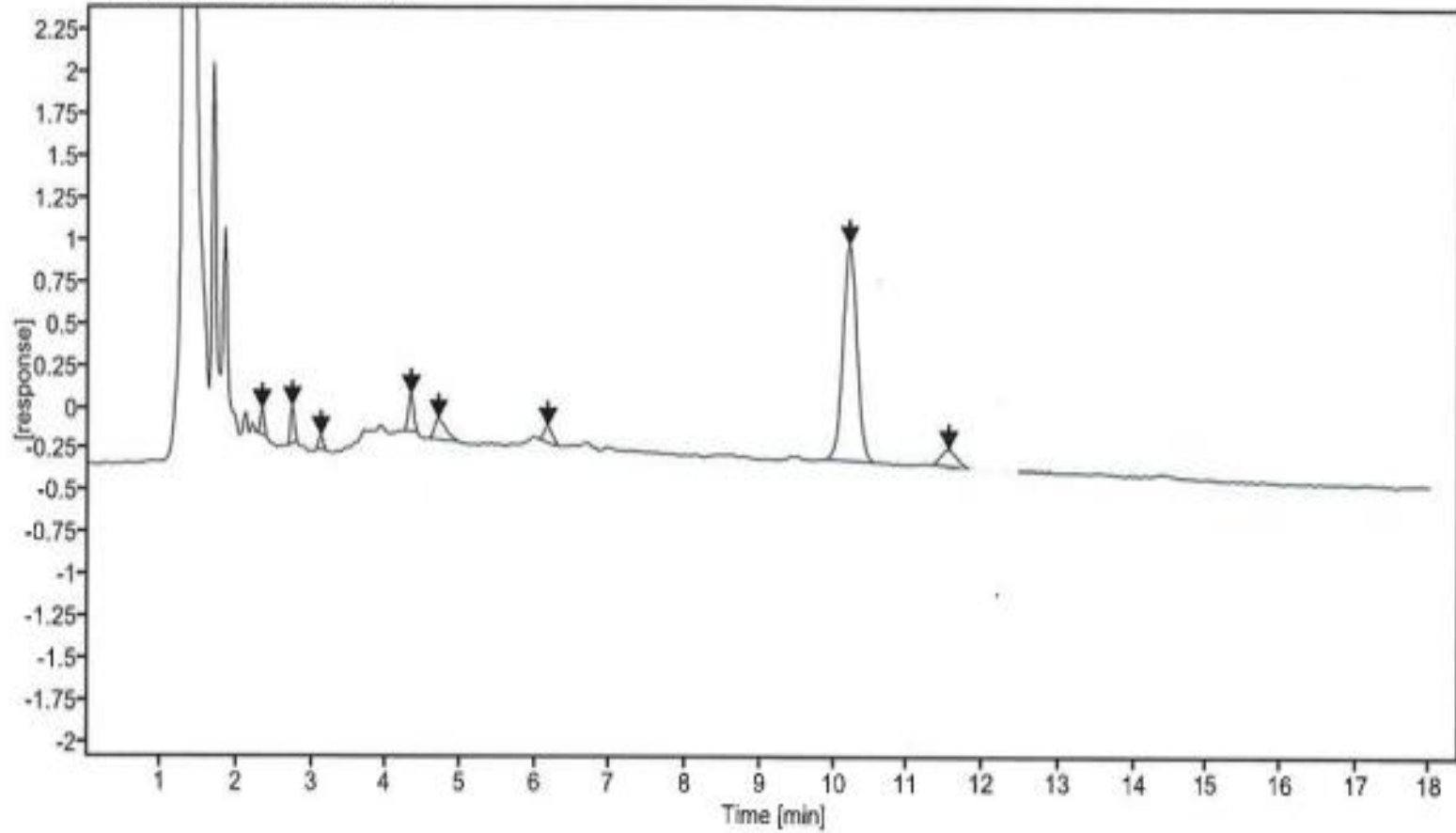
# Example

- Product development: Fentanyl 0,05 mg/ml syringes
  - Qualification of primary packaging material
  - Shelf life (content, pH, appearance, related substances)

- After 1 year: out of specification!
  - Related to fentanyl?
  - Related to our syringes?



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# What's next?

- Possible leachables
- Limited capacity and resources
- Risk assessment
  
- Qualification tests?



# Take home messages

- Qualification of primary packaging materials provides insight into presence of leachables and extractables
- Take your final product into account!

