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# MICROBIOLOGICAL PERFORMANCE QUALIFICATION OF THE ROBOTIC SYSTEMS APOTECA-SYRINGE AND APOTECA-UNIT

## Background and Importance

Fully automated robotic systems designed for the aseptic preparation of non-cytotoxic ready-to-administer (RTA) and ready-to-use (RTU) parenterals require microbiological performance qualification during the implementation process.

## Aim and Objectives

The objective of the study was the microbiological performance qualification of the fully automated robotic systems APOTECAsyringe and APOTECAunit (Loccioni, Italy) by media-fill simulations and supplemental environmental monitoring in the critical zones, followed by a cleaning procedure and 4 hour-UV radiation regarding the user manual.

## Materials and Methods

**APOTECAsyringe – Media-fill simulation; automated filled, capped, labelled**

1. **Product: Polypropylene syringe 10 mL,**
   **n = 100/day x 5 days (total: 500 syringes)**
   Content: premixed media: 1500 mL Tryptic Soy Broth Single Strength
   750 mL BD Tryptic Soy Broth Double Strength + 750 mL Aqua ad inject.

**2. Environmental monitoring**

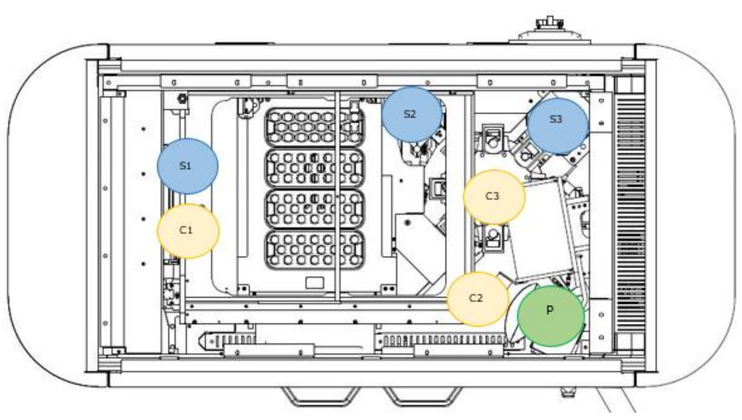


Figure 1: Type and location of environmental monitoring


Photo of APOTECAsyringe™

C1-3=contact plates, S1-3=settle plates,
P=particle counting (≥ 0.5 µm/m³, 5 µm/m³)

**APOTECAunit – Media-fill simulation; automated filled, capped, labelled**

1. **Product: Polypropylene syringe 50 mL, n = 25/day x 10 days (total: 250 syr.)**
   Content: 25 mL BD Tryptic Soy Broth Double Strength + 25 mL Aqua ad inject.

2. **Product: Polyolefine bag 100 mL, n = 25/day x 10 days (total 250 bags)**
   Content: 50 mL prefilled 0.9% NaCl infusion bag freeflex® Fresenius
   + 50 mL BD Tryptic Soy Broth Double Strength

**3. Environmental monitoring**

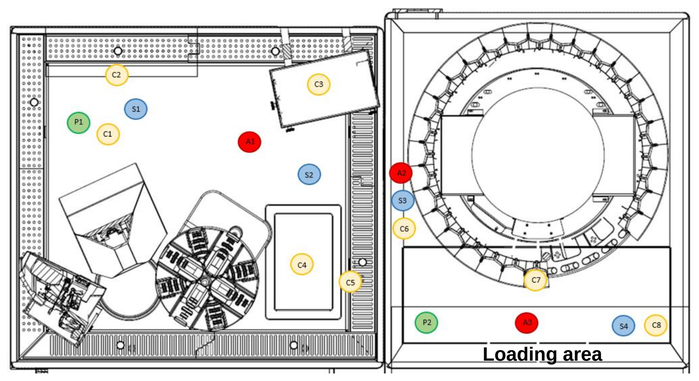


Figure 2: Type and location of environmental monitoring


Photo of APOTECAunit™

C1-8=contact plates, S1-4=settle plates, A1-3=active air sampling,
P1-2=particle counting (≥ 0.5 µm/m³, 5 µm/m³),

- **Incubation of media-fills:** At 15°C - 25°C **Analysis:** Visual inspection of turbidity; Day 7, Day 14
- **Environmental controls:** Particle counting (PZG 131); active air sampling (MAS-100 NT) and settle plates (CASO-Agar m. LT-ICR 30 mL IPC, heipha/Merck); contact plates and fingerprints (CASO-Abklatschagar Tryptic Soy Contact Agar LT-ICR, heipha/Merck)
  Sampling locations see figure 1 and figure 2
  - **Incubation of plates:** 5 - 7 days at 15°C - 25°C followed by 2 - 3 days at 30°C - 35°C
  - **Analysis:** Colony forming units (CFU) counting, particle counting; acceptance criteria: EU-GMP Guide, Annex 1 (2007)

## Results

### APOTECAsyringe

**Table 1: Results of visual inspection of media-fill products and supplemental environmental monitoring**

CFU=colony forming units, FR=fingerprints right hand, FL=fingerprints left hand.

| | Media-fill products | | Environmental Monitoring - type and location | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Turbidity | | Fingerprints [CFU/plate] | | Contact plates [CFU/plate] | | | Settle plates [CFU/plate] | | | Particles [µm/m³] | |
| | Day 7 | Day 14 | FR | FL | C1 | C2 | C3 | S1 | S2 | S3 | ≥ 0,5 | ≥ 5 |
| Day 1 | None | None | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 69 | 1 |
| Day 2 | None | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Day 3 | None | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 |
| Day 4 | None | None | 1 | 0 | 3 | 0 | 1 | 0 | 0 | 0 | 85 | 0 |
| Day 5 | None | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 30 | 1 |
| **Mean** | - | - | **0.2** | **0** | **0.6** | **0** | **0.6** | **0** | **0** | **0.2** | **37.4** | **0.6** |

### APOTECAunit

**Table 2: Results of visual inspection of media-fill products and supplemental environmental monitoring**

CFU=colony forming units, FR=fingerprints right hand, FL=fingerprints left hand.

| | Media-fill products | | Environmental Monitoring – type and location | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Turbidity | | Fingerprints [CFU/plate] | | Contact plates [CFU/plate] | | | | | | | | Settle plates [CFU/plate] | | | | Active air sampeling [CFU/plate] | | | No. Particles [µm/m³] | | | |
| | | | | | | | | | | | | | | | | | | | | P1 | | P2 | |
| | Day 7 | Day 14 | FR | FL | C1 | C2 | C3 | C4 | C5 | C6 | C7 | C8 | S1 | S2 | S3 | S4 | A1 | A2 | A3 | ≥ 0,5 | ≥ 5 | ≥ 0,5 | ≥ 5 |
| Day 1 | None | None | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 24 | 2 | 24 | 1 |
| Day 2 | None | None | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 10 | 12 | 5 | 17 | 0 |
| Day 3 | None | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | n.a. | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 35 | 4 | 15 | 1 |
| Day 4 | None | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 74 | 3 | 0 | 0 |
| Day 5 | None | None | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 0 | 81 | 8 |
| Day 6 | None | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 22 | 2 | 10 | 0 |
| Day 7 | None | None | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 19 | 0 |
| Day 8 | None | None | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 29 | 1 |
| Day 9 | None | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 37 | 3 | 7 | 0 |
| Day 10 | None | None | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 7 | 2 |
| **Mean** | - | - | **0.6** | **0** | **0** | **0.1** | **0** | **0.1** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0.2** | **0** | **0.1** | **1** | **22** | **1.9** | **20.9** | **1.3** |

None of the 1.000 media-fill products showed turbidity when inspected after 7 and 14 days of incubation, thereby indicating no growth of microorganisms.

CFU counts and particle numbers met the acceptance criteria of EU-GMP Guide, Annex 1 (2007), cleanroom class A, except loading area (cleanroom class B).

## Conclusion

The fully automated robotic systems APOTECAsyringe and APOTECAunit passed the microbiological performance qualification.

Both robotic systems allow safe automated aseptic preparation of non-cytotoxic RTA and RTU parenteral products.