A new Industry Standard for Automated Fill & Finish of Small Batches

European Aseptic Conference

#sharing challenges and solutions in practice

Part of PharmaCongress – Düsseldorf/Neuss, 31 May–1 June 2022

Supported by

Speakers.

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Content.

1 01 | Background

2 02 | Requirements & Expectations

3 03 | Features

4 04 | Current status

5 05 | Summary

Content.

1 01 | Background

2 02 | Requirements & Expectations

3 03 | Features

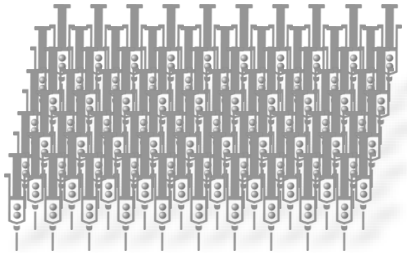
4 04 | Current status

5 05 | Summary

Opposite trends.

SMALL SCALE

batch sizes vary between 500 and 3.000 units



LARGE SCALE

Small scale injectable filling.

SMALL SCALE

The technical and economic challenge for high value drugs in smaller batch sizes is to maximize API-yield, flexibility and time-to-market.

- **Great attention to yield**
- **Fast decontamination**
- **Fast batch changeover**
- **Flexible filling concepts**

Small scale injectable filling.

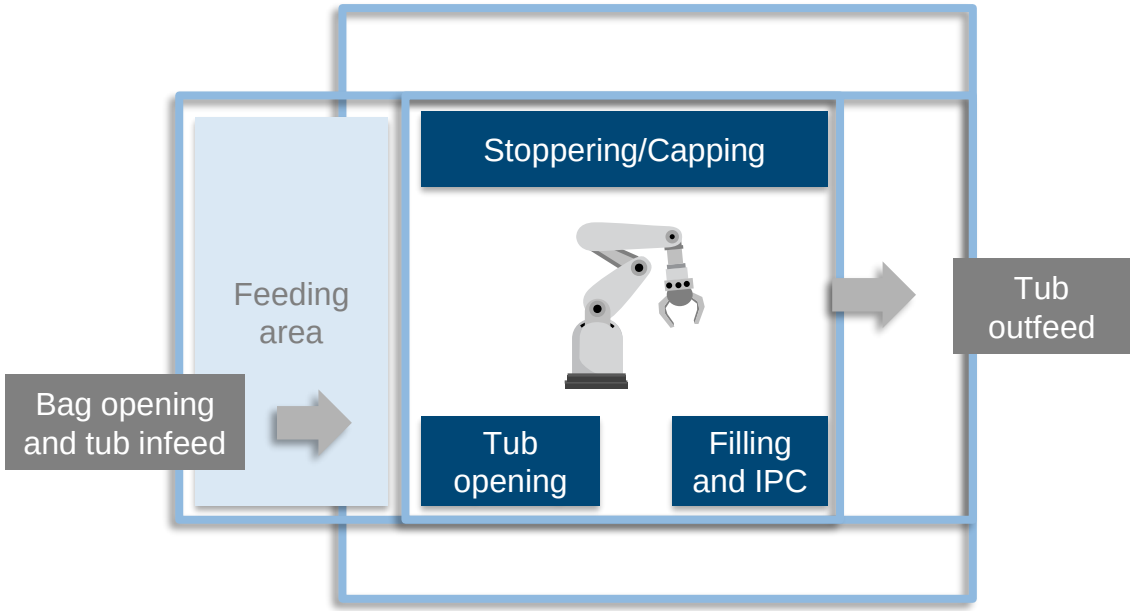
SMALL SCALE

Common production lines, optimized for quantities in the six or seven-digit range are largely unsuitable for meeting these new requirements.

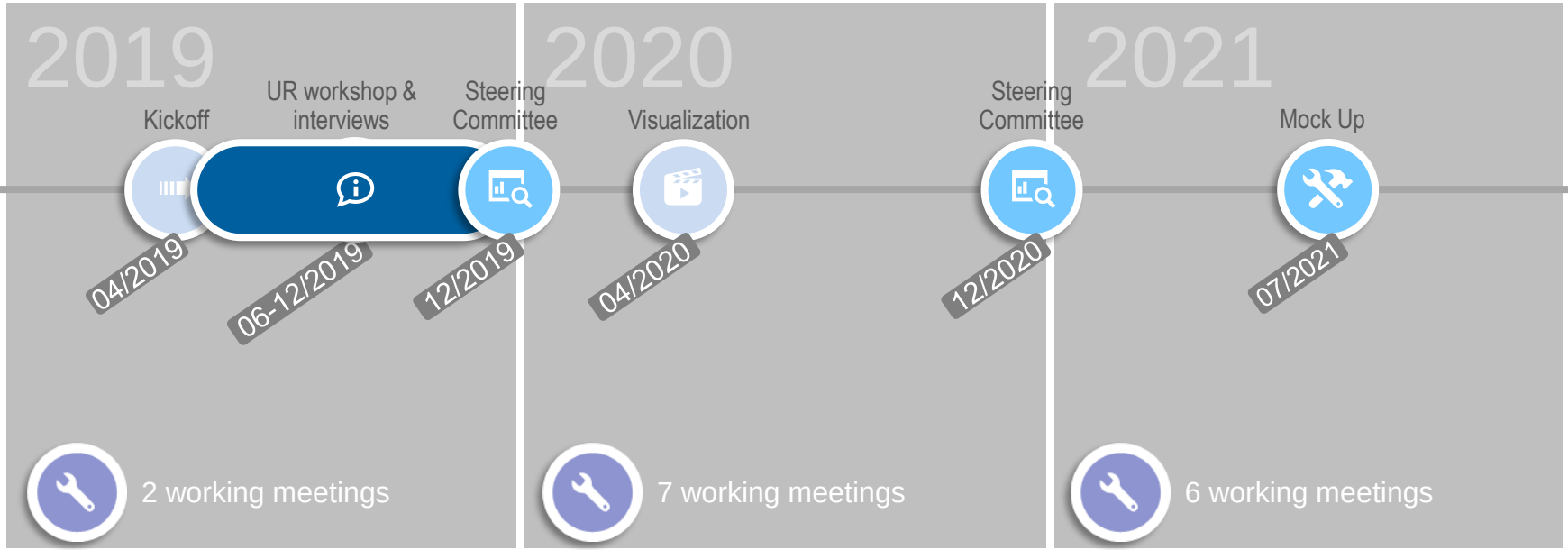
Small scale injectable filling.

Development of an innovative cGMP-compliant and flexible production cell based on isolator technology

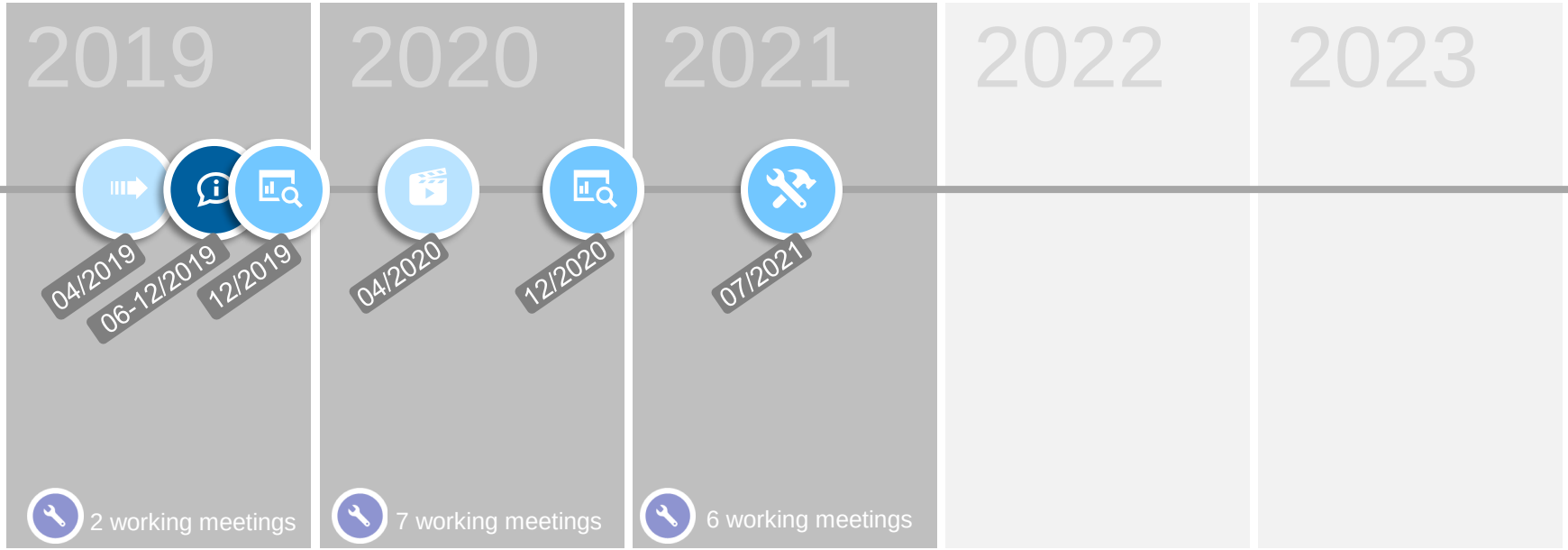
Small scale injectable filling.



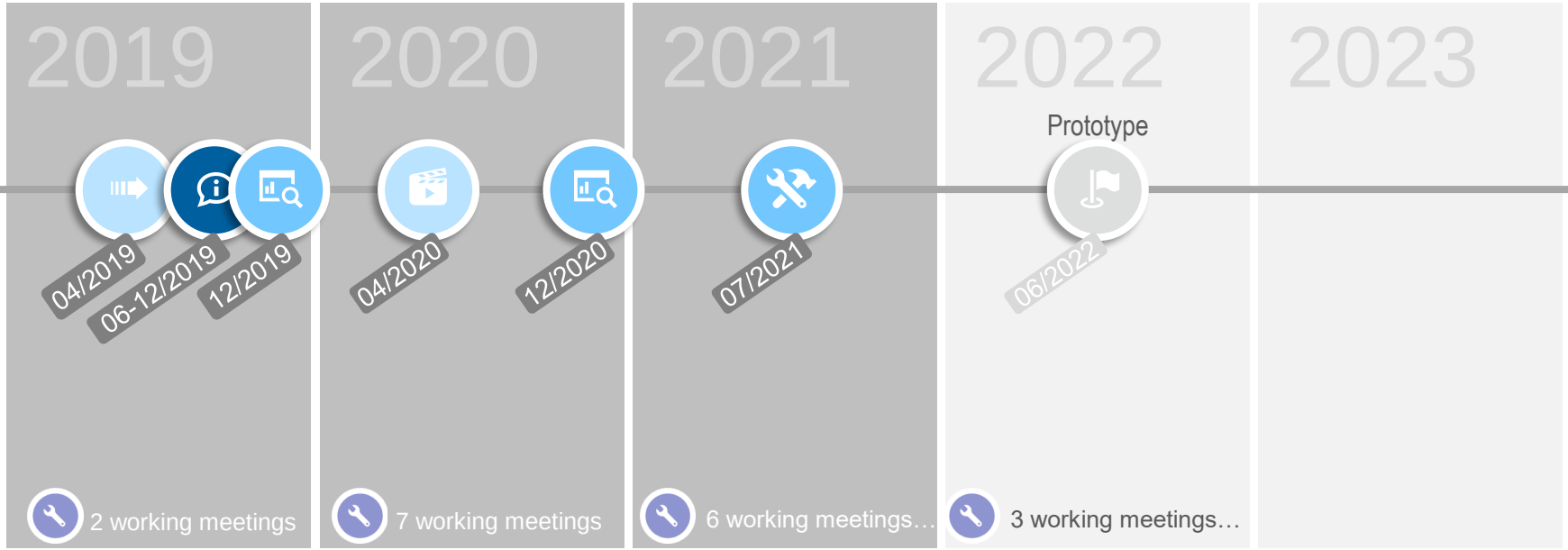
What happened so far…



What happened so far…



…and how we go on.



Content.

1 01 | Background

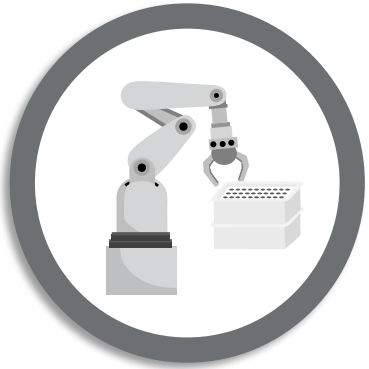
2 02 | Requirements & Expectations

3 03 | Features

4 04 | Current status

5 05 | Summary

Requirements.



Great attention to yield

for small quantities, losses are particularly significant

Fast decontamination

short H_2O_2 decontamination cycles for using the cleanroom efficiently

Fast batch changeover

large number of small batches to be filled require short set-up and cleaning times

Flexible filling concepts

use exactly the format that is required for the respective high-quality product

Regulatory expectations.

FDA Guidance

The design of equipment used in aseptic processing should **limit** the number and complexity of aseptic **interventions by personnel.** (…) Automation of other process steps, including **the use of technologies** such as **robotics**, can further **reduce risk to the product.**

No aseptic interventions by personnel – even no set-up.

Instead, robotics will take over all main activities.

R. Friedman: "Use of robotics in aseptic processing has the potential to profoundly reduce contamination risks"

Source: FDA Guidance for Industry Sterile Drug Products, produced by aseptic processing cGMP, Sept. 2004

Mockup vector created by upklyak

Regulatory expectations.

Annex 1 draft

So, what are we expecting?

Our expectation is that the contact parts (direct and indirect) are sterilised using a robust sterilisation method that meets the current requirements of annex 1. This means that:

the sterilising agent reaches all of the critical surfaces in a consistent and repeatable manner, typically requiring processes such as moist or dry heat sterilisation.

the item is unloaded from the sterilisation process either wrapped in integral covering or container, or is transferred under grade A conditions, such as a transfer isolator into the manufacturing isolator.

We also expect that the parts are not exposed to the isolator environment until the isolator has been closed and after completion of the work zone decontamination VHP cycle.

The steam sterilized equipment is unloaded into a H_2O_2 decontaminated grade A.

Unloading into a grade A environment, no VHP cycle after set-up!

Source: Andrew Hopkins, MHRA Inspectorate Blog, commenting on EU, Annex 1 draft
https://mhrainspectorate.blog.gov.uk/2018/04/20/vhp-vapour-hydrogen-peroxide-fragility/
Mockup vector created by upklyak

Content.

1 01 | Background

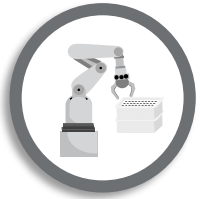
2 02 | Requirements & Expectations

3 03 | Features

4 04 | Current status

5 05 | Summary

Features.

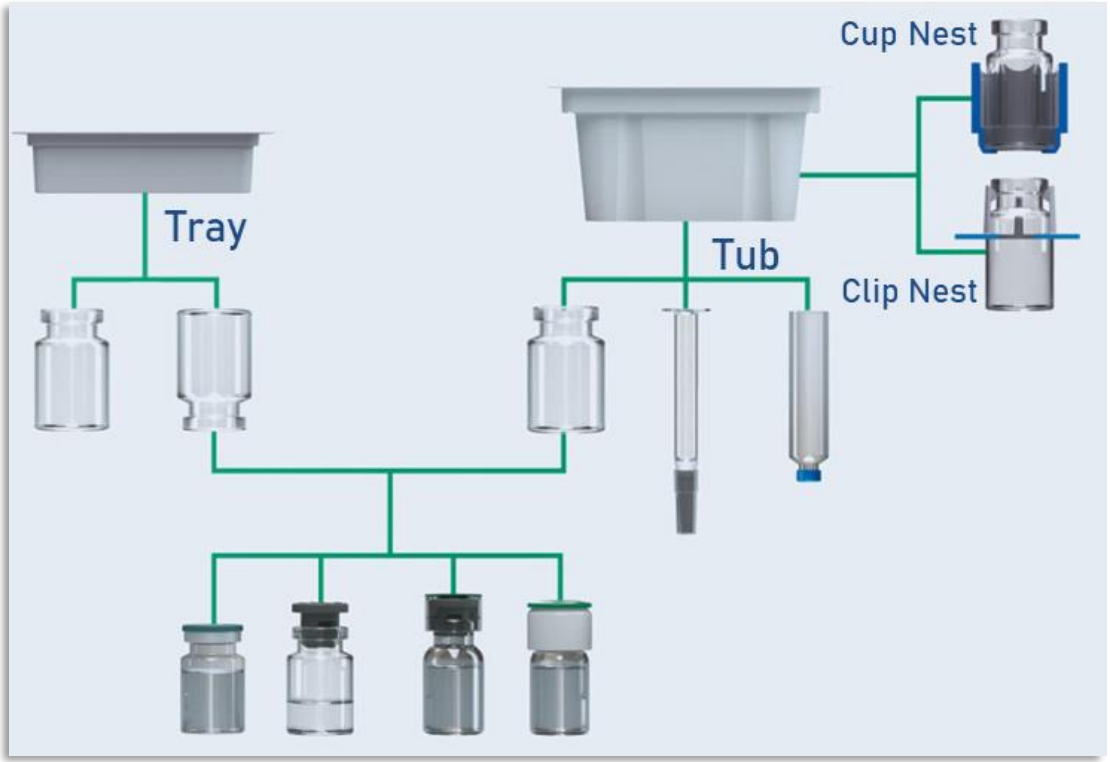


Flexible filling concepts

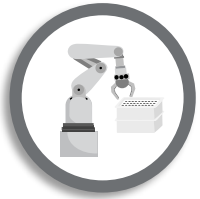
the system can process different RTU formats in the tub and in the tray

beside vials, cartridges and syringes can also be filled

Huge variety of stoppers has been considered



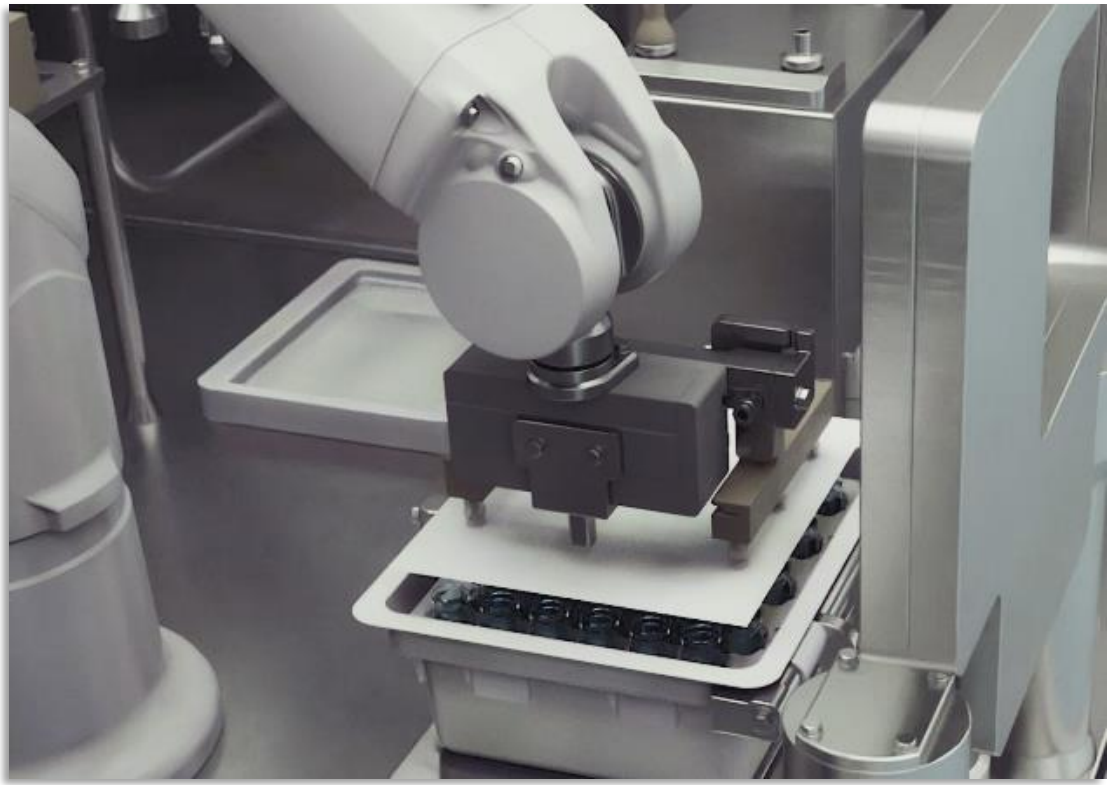
Fast batch changeover.



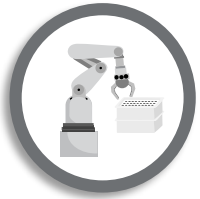
Fast batch changeover

smart gripper solutions in combination with integrated robotics reduce format parts to a minimum

negligible time aspect of format part exchange



Fast decontamination.

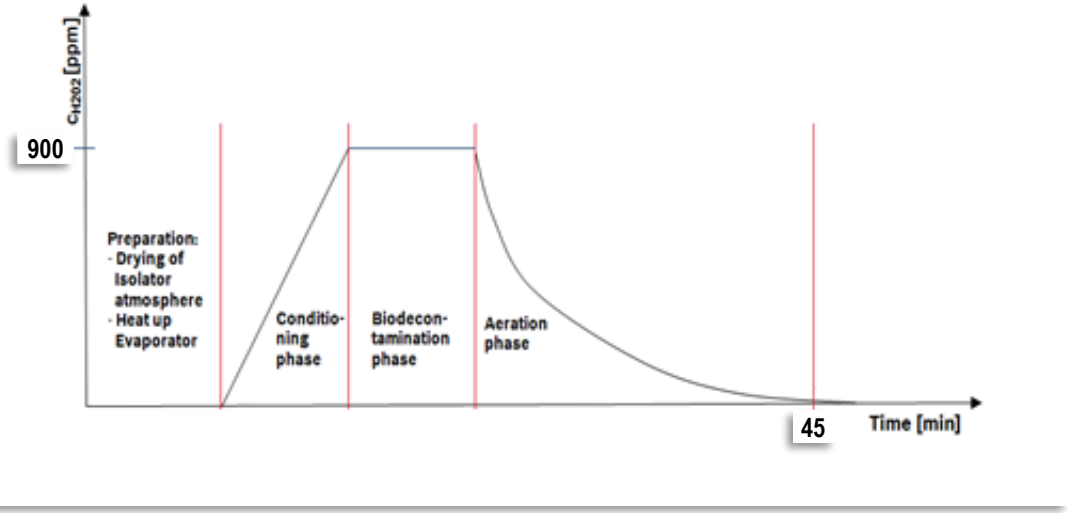


Fast decontamination

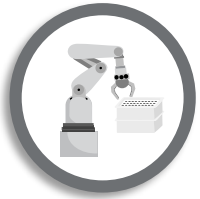
machine setup after decontamination

packaging material is introduced after decontamination

goal: 45 min for complete cycle time down to 1 ppm



Great attention to yield.

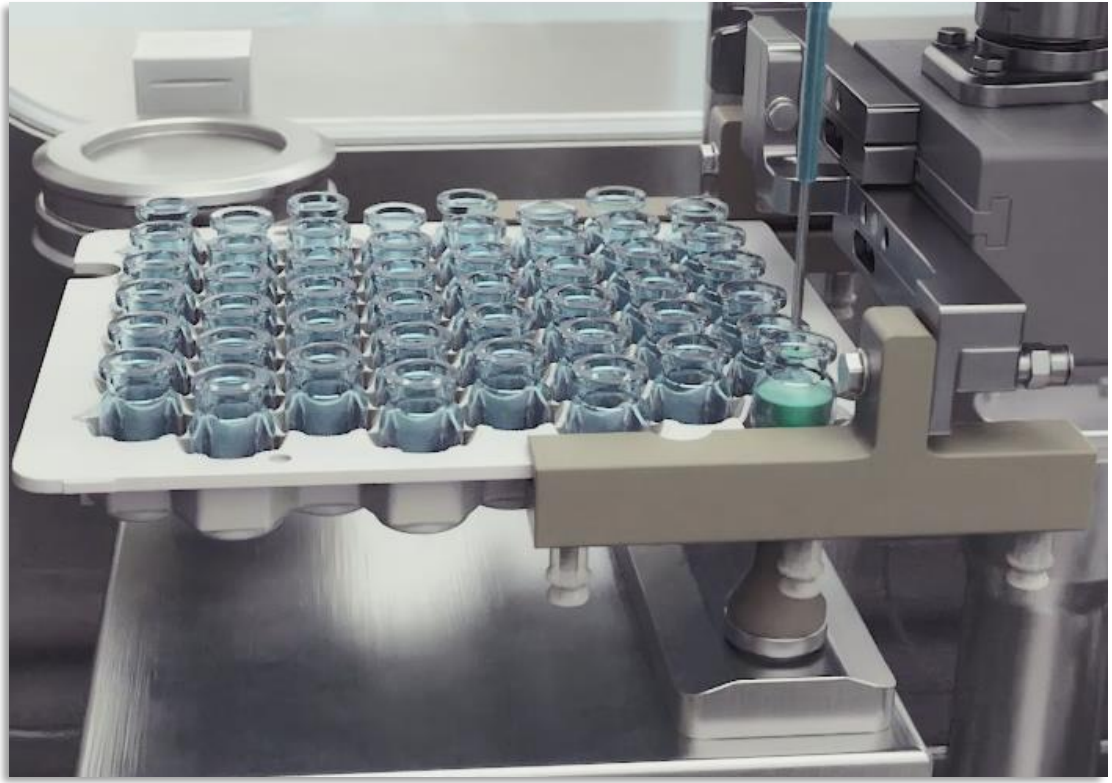


Great attention to yield

losses can be reduced to a minimum

100 % fill weight check up to the last unit

weighing system can also operate in statistical sampling mode



Content.

1 01 | Background

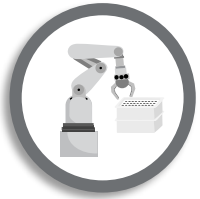
2 02 | Requirements & Expectations

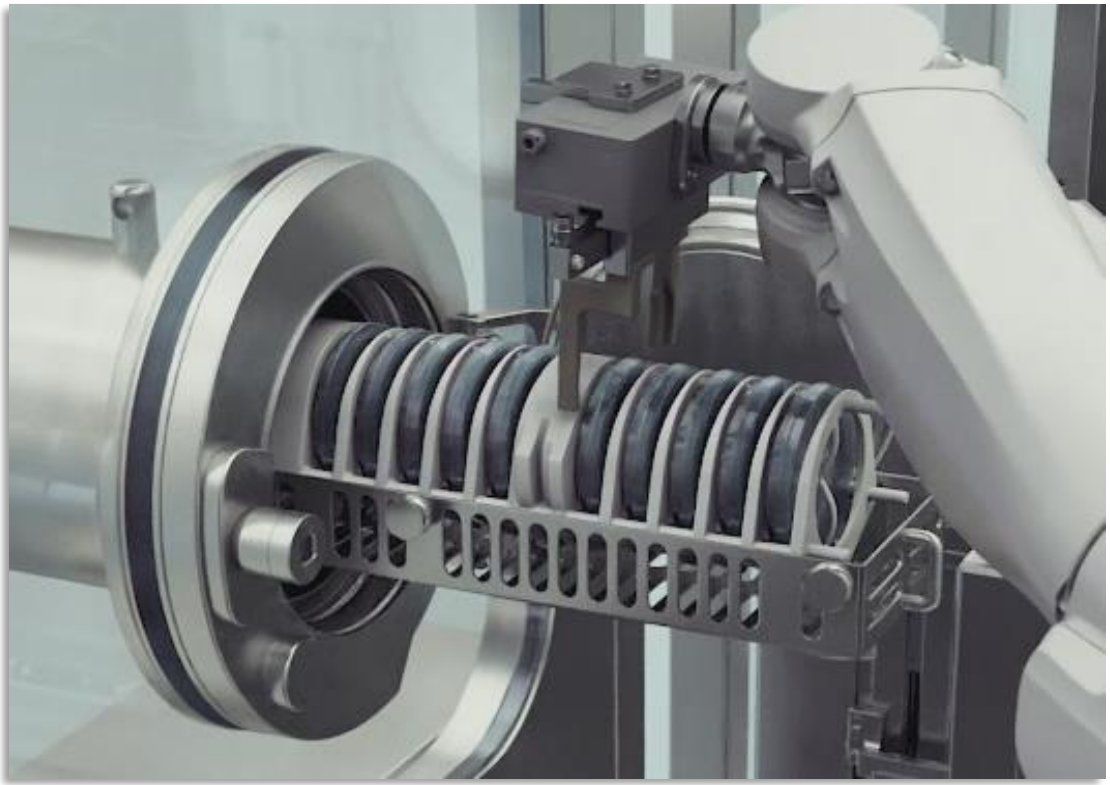
3 03 | … and more features

4 04 | Current status

5 05 | Summary

Monitoring.



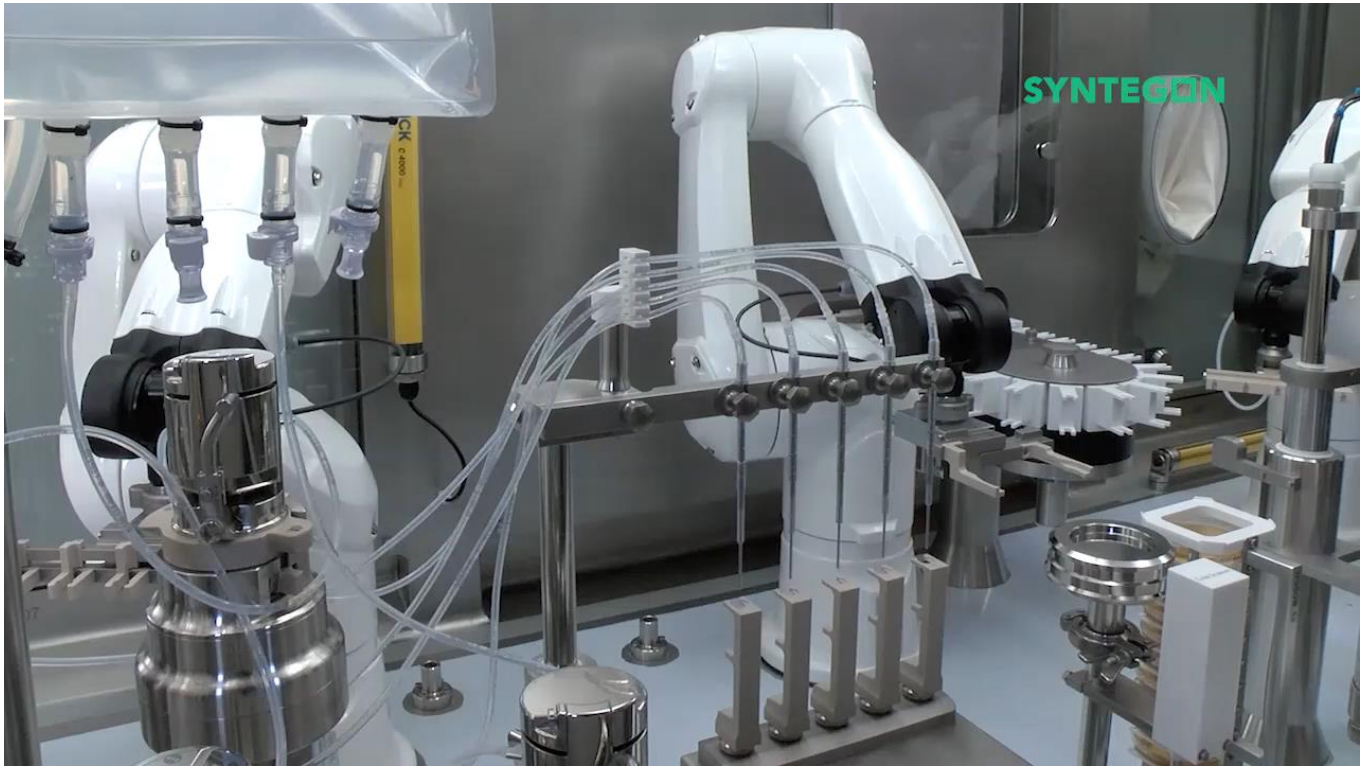


Monitoring

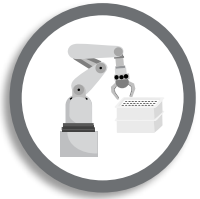
infeed of disposable rack via RTP-port

microbiological monitoring plates are automatically removed from the rack

Automated monitoring.



Alternative monitoring system.

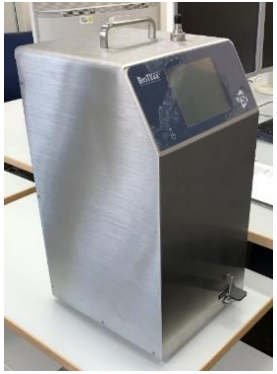


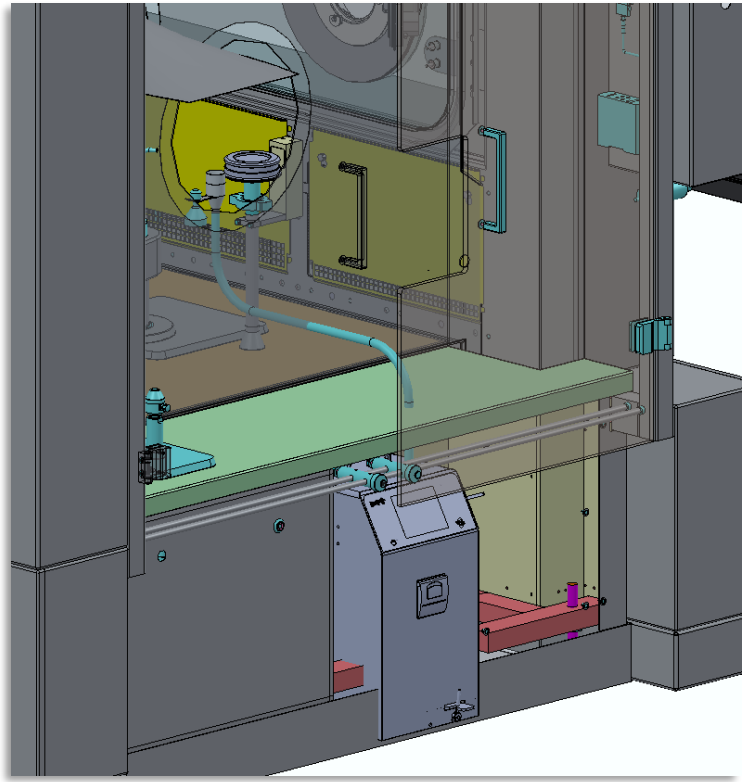
Alternative monitoring system

prepared for real-time monitoring

picture shows Biotrak device

currently under evaluation





Content.

1 01 | Background

2 02 | Requirements & Expectations

3 03 | Features

4 04 | Current status

5 05 | Summary

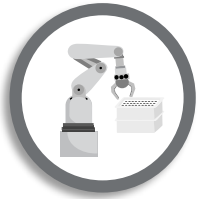
Mock-up.

Mock-up

July 2021, first mock-up of the prototype at Syntegon

handling within the isolator was carefully reviewed using the model

Positioning in Vetter’s production

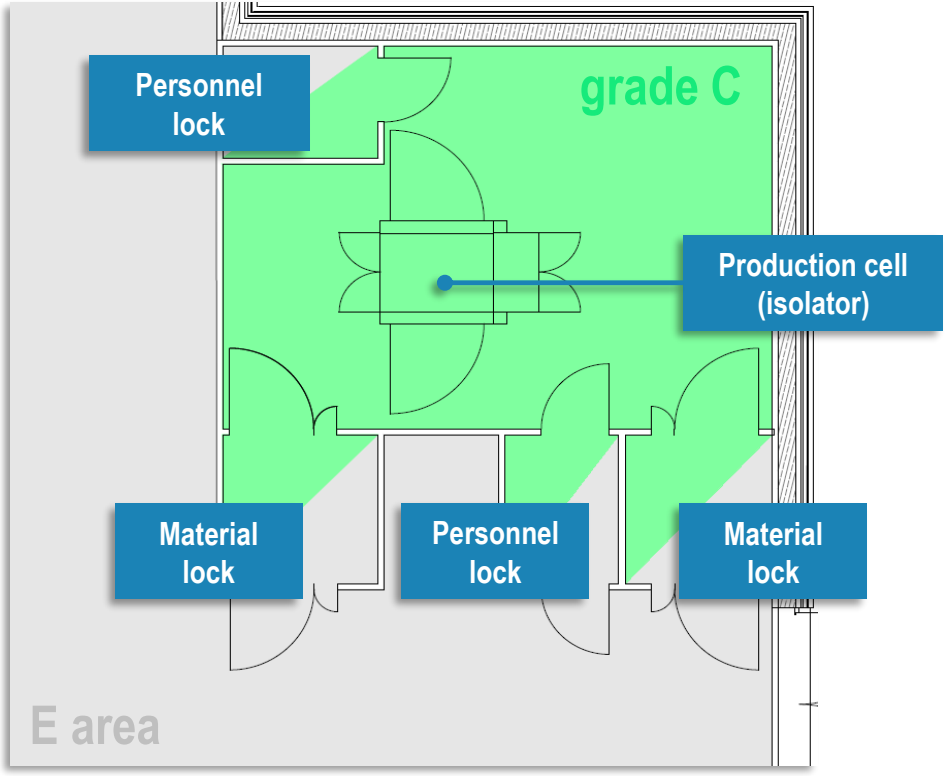


Positioning in Vetter’s production

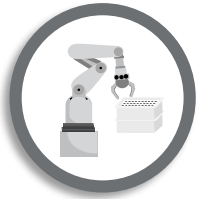
Integration in an existing production building

Installation in grade C

One-way lock concept for personnel and material



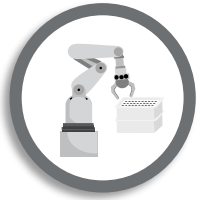
Commissioning.



Commissioning

Virtual commissioning for expediting project schedule

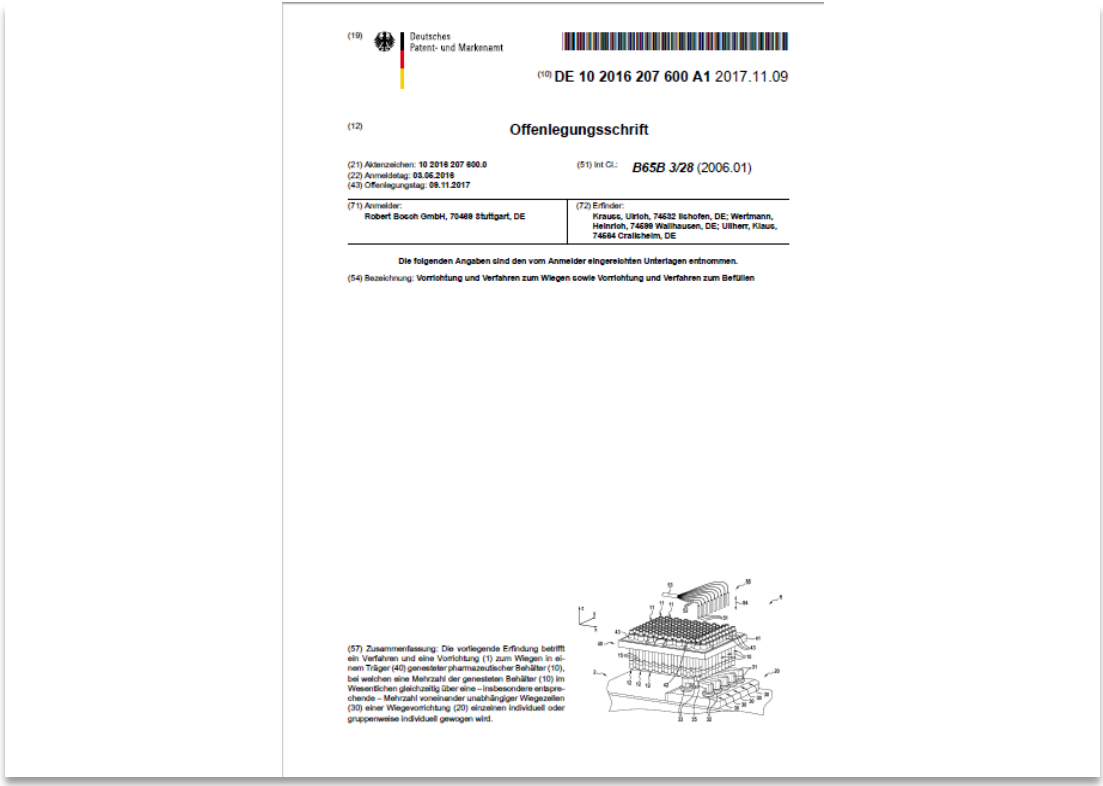
Patent application.



Patent application

multiple patent applications in progress

focus on processes for operating gloveless isolators



(19) Deutsches Patent- und Markenamt

(10) **DE 10 2016 207 600 A1** 2017.11.09

(12) **Offenlegungsschrift**

(21) Aktenzeichen: **10 2016 207 600.0**
(22) Anmeldetag: **03.06.2016**
(43) Offenlegungstag: **09.11.2017**

(51) Int Cl.: ***B65B 3/28*** (2006.01)

(71) Anmelder:
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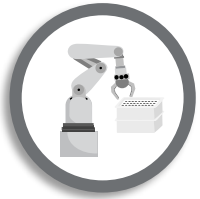
Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen.

(54) Bezeichnung: **Vorrichtung und Verfahren zum Wiegen sowie Vorrichtung und Verfahren zum Befüllen**

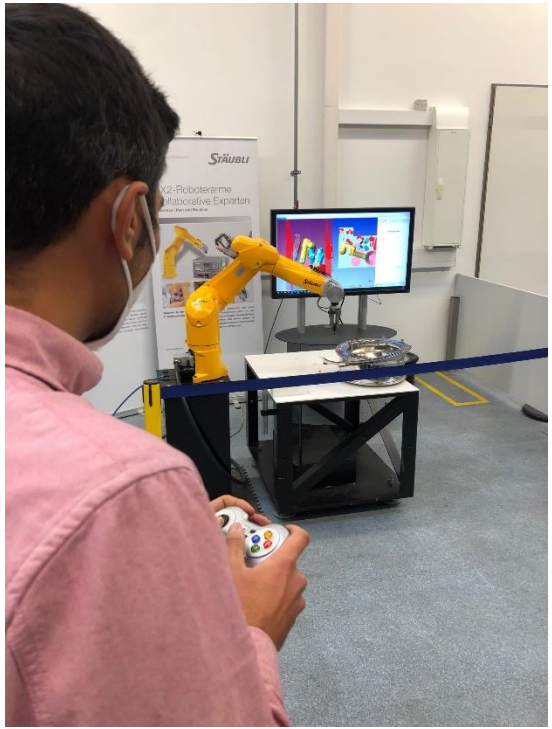
(57) Zusammenfassung: Die vorliegende Erfindung betrifft ein Verfahren und eine Vorrichtung (1) zum Wiegen in einem Träger (40) genesteter pharmazeutischer Behälter (10), bei welchen eine Mehrzahl der genesteten Behälter (10) im Wesentlichen gleichzeitig über eine – insbesondere entsprechende – Mehrzahl voneinander unabhängiger Wiegezellen (30) einer Wiegevorrichtung (20) einzeln individuell oder gruppenweise individuell gewogen wird.

Tele-operation

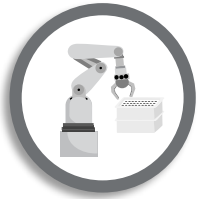


Tele-operation

tests for tele-operation for trouble shooting are ongoing



Assembly



Assembly

Isolator is mounted on machine

Machine is currently under start-up phase

Benefits from virtual commissioning

Content.

1 01 | Background

2 02 | Requirements & Expectations

3 03 | … and more features

4 04 | Current status

5 05 | Summary

Summary.

- New drug pipeline is asking for new, fill/finish solutions with more focus on yield and flexibility than on output.
- For this segment, a gloveless isolator could become state-of-the-art.
- Robotics and standardization are the key for achieving this goal.
- In every respect, the present concept corresponds to the regulatory requirements.

Thank you for your attention

QUESTIONS ?

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