Implementation of Biofluorescence Particle Counters to Replace Traditional EM Methods

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Novo Nordisk A/S

Novo Nordisk at a **glance**

Novo Nordisk is a leading global healthcare company, founded in 1923 and headquartered in Denmark.

We are constantly looking for ways to improve increasingly difficult production processes and ensure delivery of products for our patients now and in the future

Our purpose is to drive change to defeat diabetes and other serious chronic diseases such as obesity and rare blood and endocrine disorders.

We do so by pioneering scientific breakthroughs, expanding access to our medicines and working to prevent and ultimately cure disease.

Products marketed in
170
countries

Total net sales
176.9
billion DKK

Affiliates in
80
countries

Supplier of nearly
50%
of the world's insulin

More than
36
million people use our diabetes care products

R&D centres in China, Denmark, India, UK and US

Strategic production sites in Denmark, Brazil, China, France and US

Around
55,000
employees

Growth disorders

Rare bleeding disorders

Diabetes

Obesity

IY 20 23
Driving change for generations

Agenda

1. **General Background and Application**
2. Validation Strategy
3. Operational Strategy
4. Roadmap and Learnings

Why change?

Goal

Zero humans in grade A

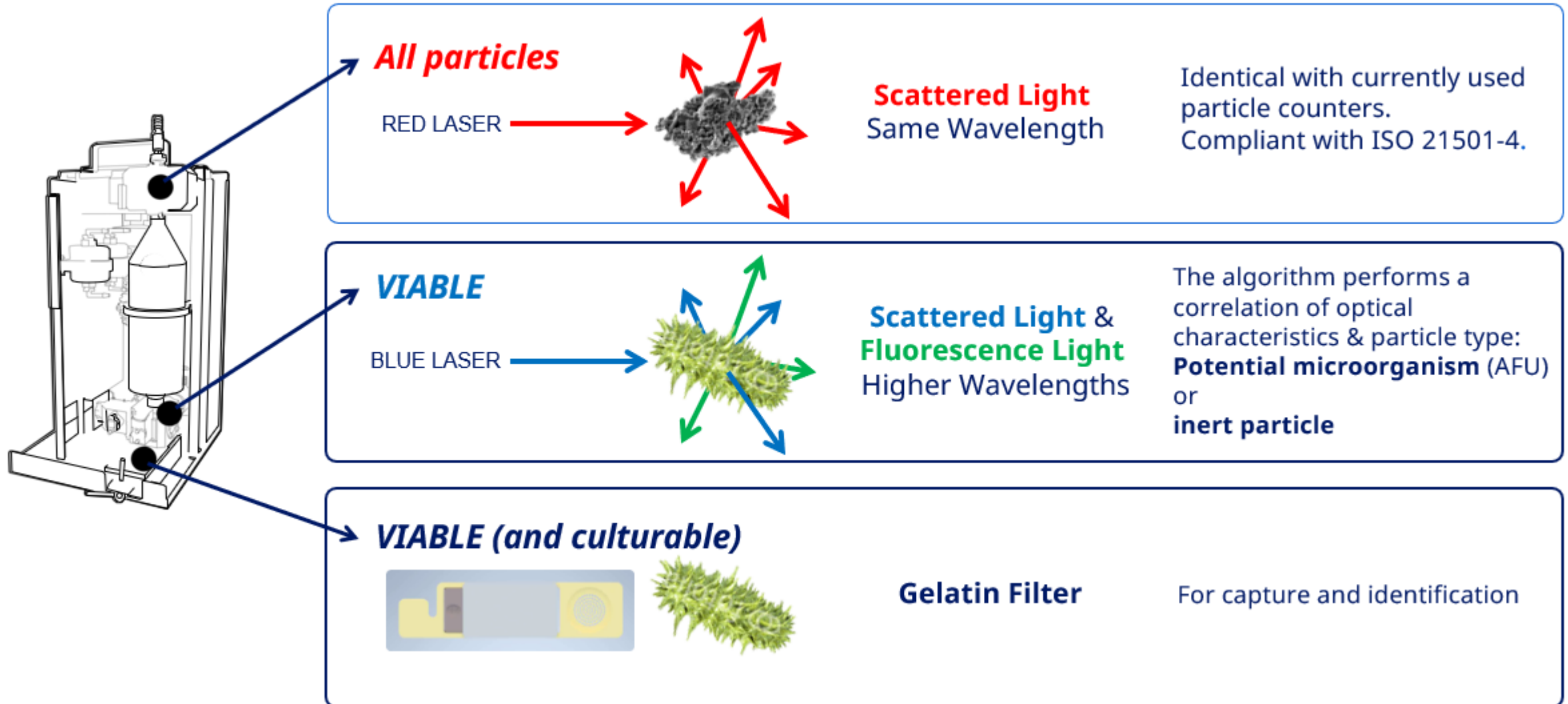**Automated grade A areas**

BioTrak = Active Air + Particle Counter + Settle Plate
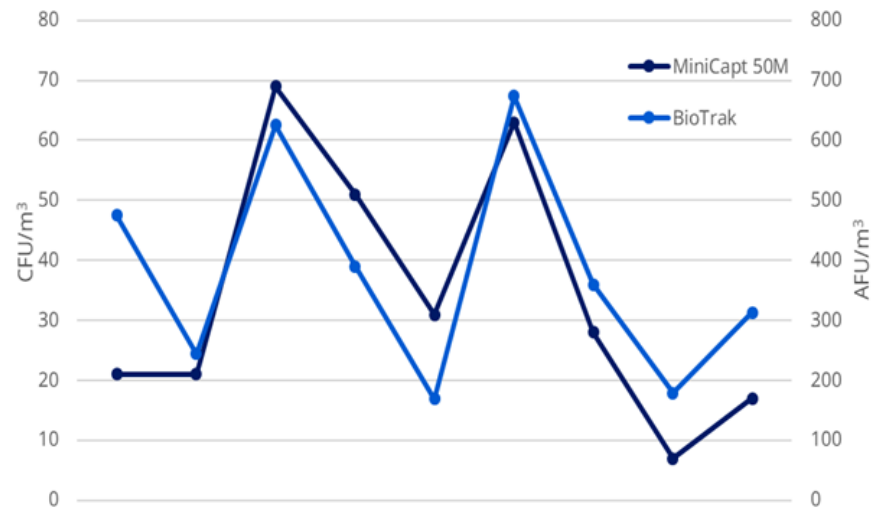
Biofluorescence Particle Counters

- No interventions for EM-sampling

- Active and continuous air monitoring

- Real time results giving the opportunity to investigate immediately

- Improved sterility assurance

What is a BioTrak?

All particles

RED LASER →

Scattered Light Same Wavelength

Identical with currently used particle counters. Compliant with ISO 21501-4.

VIABLE

BLUE LASER →

Scattered Light & **Fluorescence Light** Higher Wavelengths

The algorithm performs a correlation of optical characteristics & particle type: **Potential microorganism** (AFU) or **inert particle**

VIABLE (and culturable)

Gelatin Filter

For capture and identification

Preliminary tests

Comparison of viable counts in grade D

Parallel monitoring with BioTrak and active air. Primary Y-axis is CFU and secondary is AFU with a factor 10 difference.

Conclusion:
- ✓ BioTrak is more sensitive compared to traditional growth based methods

Comparison of viable counts in grade A

Case 1: Isolator filling line. 10 hours after end of production (at rest).

Channel	Min	Max	Average	Std. Dev.	Std.Error
0,5 µm Viable	0	0	0	0	0
5,0 µm Viable	0	0	0	0	0

Case 2: RABS filling line. 8 hours fill, normal operation conditions.

Channel	Min	Max	Average	Std. Dev.	Std.Error
0,5 µm Viable	0	0	0	0	0
5,0 µm Viable	0	0	0	0	0

Case 3: Conventional filling line. 48 hours, normal operation conditions.

Channel	Min	Max	Average	Std. Dev.	Std.Error
0,5 µm Viable	0	0	0	0	0
5,0 µm Viable	0	0	0	0	0

Conclusion:
- ✓ No false positives and unexpected background noise
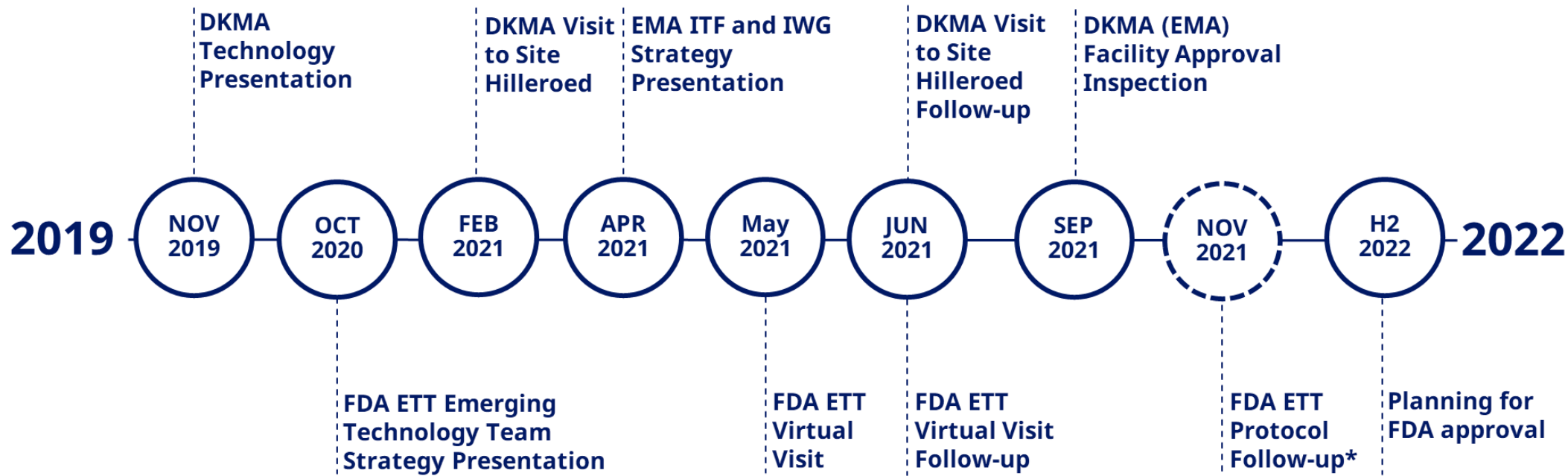- ✓ The results match existing trend for viables in air in grade A

How was the technology applied

- 2 high volume isolator filling lines (600 cartridges per minute)
- Isolator line with gloves and RTP ports
- MAS-100 ® active air samplers, Airnet particle counters
- BioTraks installed in 7 positions based on Risk Assessment
- Software integrated with the filling line to fully automate operation
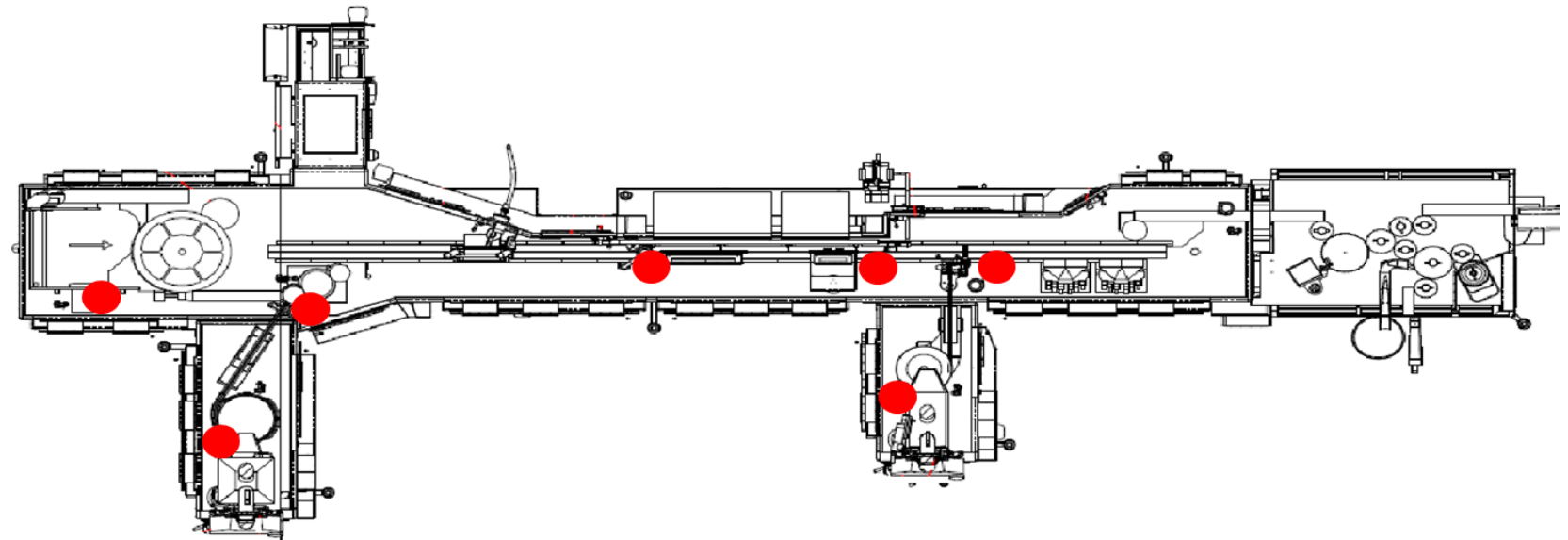
Interaction with Regulators

AFU vs CFU
Validation
ID
Calibration etc.

Novo Nordisk®

DKMA Technology Presentation

DKMA Visit to Site Hilleroed

EMA ITF and IWG Strategy Presentation

DKMA Visit to Site Hilleroed Follow-up

DKMA (EMA) Facility Approval Inspection

Dec 2022

2019 — NOV 2019 — OCT 2020 — FEB 2021 — APR 2021 — May 2021 — JUN 2021 — SEP 2021 — NOV 2021 — H2 2022 — **2022**

FDA ETT Emerging Technology Team Strategy Presentation

FDA ETT Virtual Visit

FDA ETT Virtual Visit Follow-up

FDA ETT Protocol Follow-up*

Planning for FDA approval

*Email communication only – no meeting

Slide 8

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Qualification at Novo Nordisk

Supplier Qualification

Review of supplier's Primary Validation and QA approval

- ✓ Physical Efficiency
- ✓ Accuracy
- ✓ Precision
- ✓ Specificity
- ✓ Limit of Detection (LoD)
- ✓ Limit of Quantitation (LoQ)
- ✓ Range
- ✓ Linearity
- ✓ Ruggedness (USP <1223>)
- ✓ Robustness

End User Qualification

Validation Plan

- User Requirement Specification
- **Installation/Operation Verification**
- **Interference & false count in grade A**
- **Non-inferiority in grade D and A**
- Risk/benefit

Ph. Eur. 5.1.6 - Alternative Methods for Control of Microbiological Quality including the parameters
USP<1223> - Validation of Alternative Microbiological Methods
PDA Technical Report No.33 - Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods

Qualification at Novo Nordisk
- examples

Qualification of pipes

Probe	Particle Size	Counting Efficiency
MDL1	0.5 µm	104.1%
	5.0 µm	107.6%
MDL2	0.5 µm	101.7%
	5.0 µm	99.0%
MDL3	0.5 µm	104.8%
	5.0 µm	106.4%
MDL4	0.5 µm	101.0%
	5.0 µm	100.3%
MDL5	0.5 µm	100.8%
	5.0 µm	99.4%
MDL7	0.5 µm	101.8%
	5.0 µm	107.0%
MLD8	0.5 µm	104.2 %
	5.0 µm	100.7 %

Interference testing

Wipes	Interference
Pulverized Glass	Interference
Product 1	No Interference
Product 2	No Interference
Product 3	No Interference
Product 4	No Interference
Product 5	No Interference
Ethanol on cloth	No Interference
Piston	No Interference
Caps	No Interference
Autoclave Bag	No Interference
Gloves	No Interference

Qualification at Novo Nordisk
- Non-inferiority grade A (parallel study)

Non-inferiority	Sampling duration (hrs)	# of AFU alarms	# of plates with CFU	Probability of detecting an event
Closed doors[1]	3253 hours	9	0	30.5 times higher

Collection filter	Sampling duration (hrs)	# of AFU alarms	# of collection filters with CFU
Closed doors[1]	273	0	0

1) Closed door activity: Setup and filling

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Environmental Monitoring Setup In The Isolator

1. Monitoring of air both total particulates and viables: **BioTrak**

2. Surface sampling incl. gloves with agar at the end of batch or campaign

3. Improved RCA in case of an AFU count

   a. Real time results enabling immediate investigation and precise correlation of AFU counts and ongoing activities
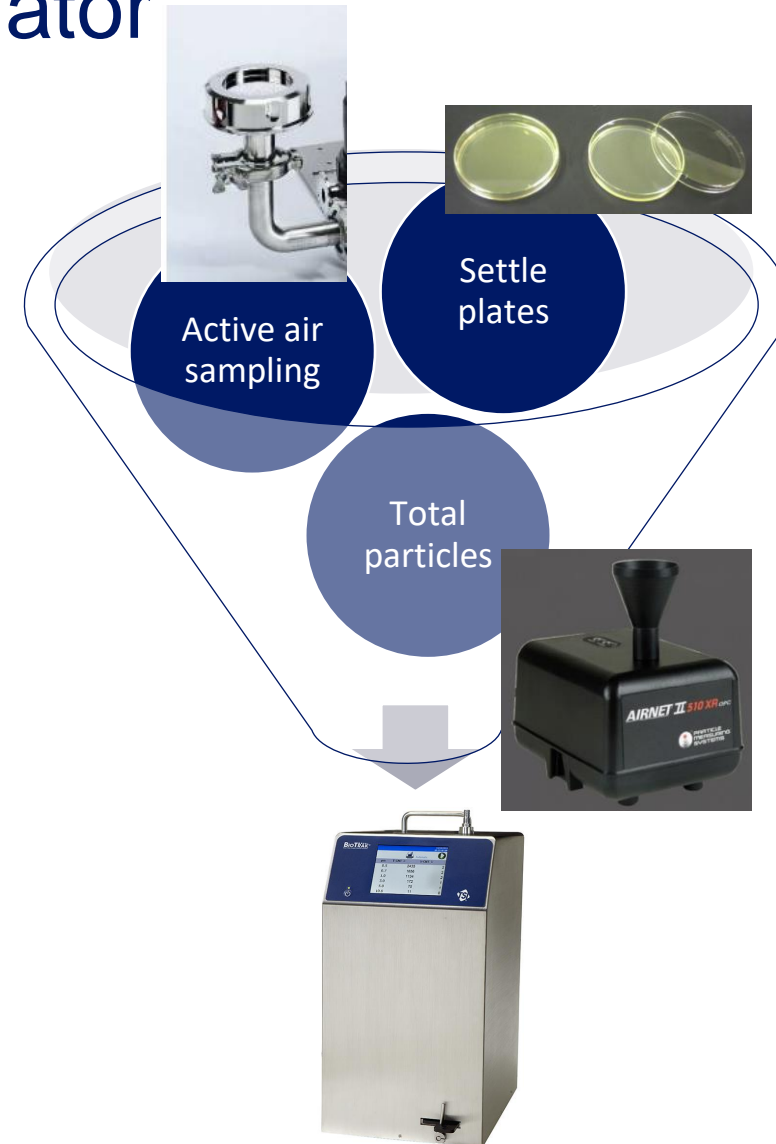
How To Handle An AFU Count?

AFU count

In grade A
AFU = CFU

Any AFU
count (>0) is
an action level

Handling of Incident

1. Immediate line stop
2. The operator is alerted, and an immediate investigation is initiated including action to collect ID[1]
3. Potentially affected units are rejected automatically

[1]ID: Incubate gelatine filter from the BioTrak

Continue fill

Following appropriate delimitation and containment

Interaction With Regulators

FDA ETT / EMA / DKMA

- Parallel study in grade A must demonstrate statistical non-inferiority

  - Study can be used for other Novo Nordisk facilities

- In-line gelatine filter must be used to get ID, only incubate in case of an AFU count

- Review raw data prior to release

- Ongoing performance/Functionality check at each batch/campaign

- Method and frequency for cleaning of piping

- Study to verify absence of VHP in piping

TEAM NOVO NORDISK

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Interaction with Regulators

Inspections so far…..

- DKMA

- FDA

- South Korea

- Türkie

What did we learn from root cause investigation ?

- **Aseptic behavior**

- **Process optimization**
  - Pressure reducing of CPE containers
  - Change of wipes

- **Set up**
  - Assembly and maintenance of pipes

Number of AFU/Batch
moving average 3 months both lines

Month
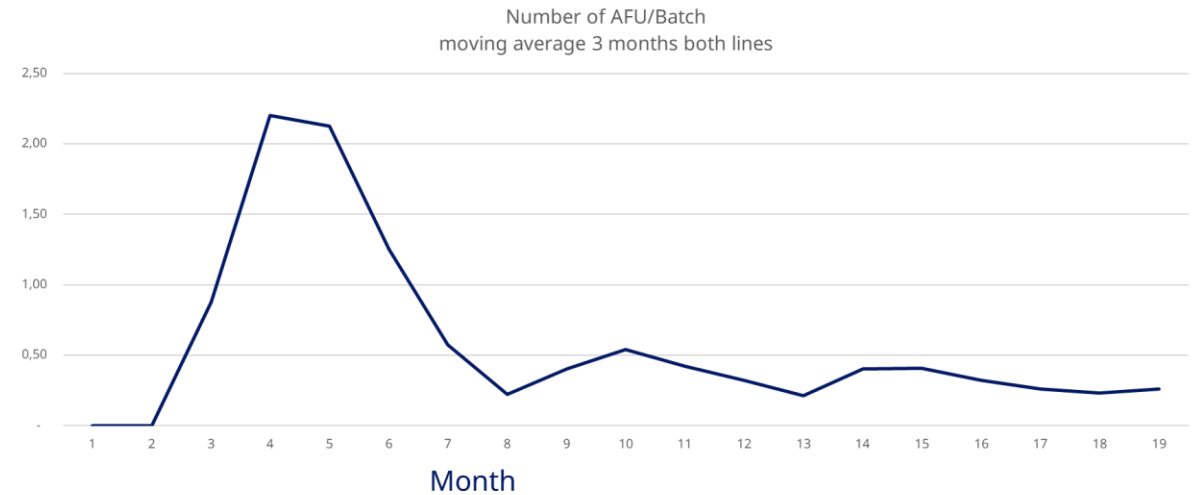
Implementing BioTrak

Goals for implementing BioTrak

- No interventions for EM-sampling

- Active and continuous air sampling

- Real time results giving the opportunity to investigate immediately

- Improved sterility assurance

After implementing BioTrak

- 80% Reduction of interventions

- 87% Reduction in filling line down time for EM-sampling

Learnings From Implementing a (new) Alternative Method

- Key to collaborate with the regulators

- The regulators are very interested in new technology

- Work with the supplier

- Expect setbacks…

Roadmap and Ambition at Novo Nordisk

- Implementation of BFPCs

Future

- Implement on other filling lines
- Automate monitoring of classified areas

2024

Operation only with BioTrak® on pilot site

From 2024

Initiate roll out on other isolator lines

Acknowledgements to The Team at Novo Nordisk A/S

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Questions?