APAS® PharmaQC – AI for culture plate reading

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BioPhorum, February 2024

CLEVER CULTURE SYSTEMS

LBT INNOVATIONS

Automated Plate Assessment System (APAS®)

Validated AI + hardware to read and interpret microbial growth on culture plates

Efficient & Scalable

Small footprint and high-throughput automation - 1 system can efficiently read up to 1,600 plates in an 8hr period

Flexible & Independent

No proprietary media - works with major media suppliers, supporting 55mm and 90mm plates

Objective & Compliant

Enduring plate image records - full data integrity and audit trail to meet your regulatory standards

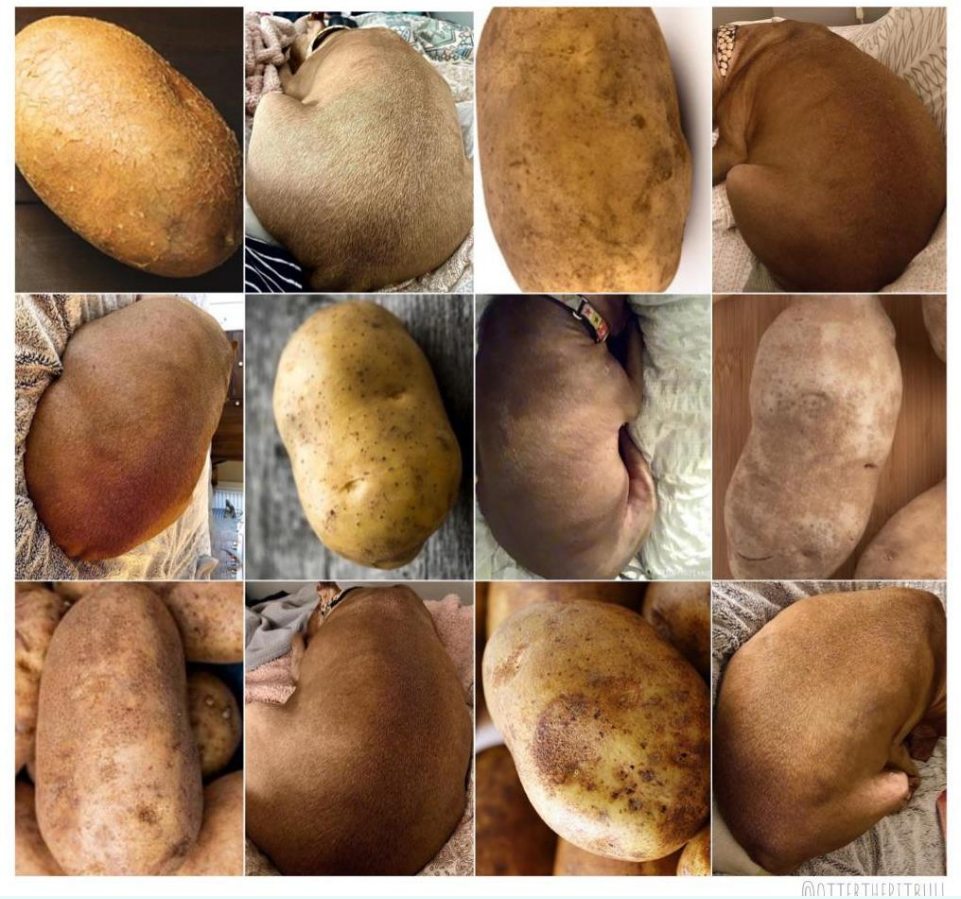
APAS® Independence Instrument

Workflow driven automation

Ensures quality and data integrity of the culture plate reading workflow

No change to existing process – positive workflow benefit through automation
– Automated validation of plate results; CFU count issued for plates with growth

Data Quality - What do you see?



Developing AI – How do you define good data?

The main factor driving the quality of an AI/ML system is the input data

- Garbage-in, garbage-out

AI systems are not normally transferable

- AI system developed for one set of hardware and/or images may not transfer to another
- Important to train for all use scenarios

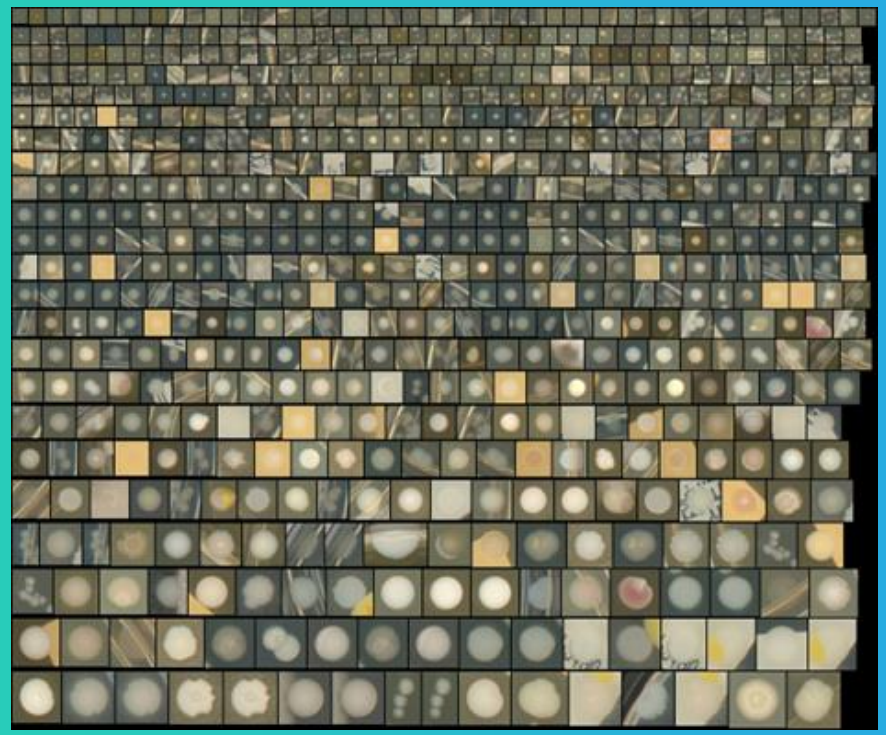
Important that data is representative of the real-world

- Needs to be controlled and authentic

Can be hard for AI companies to know if the data is ‘real’ or not

- Often don’t have in-house experts
- Data errors common in real-world, data cleaning is a big deal for AI companies

Example: Microbiology colony morphology variation



APAS PharmaQC

Ensuring robustness: Limit external influences and check every image

Uniform lighting

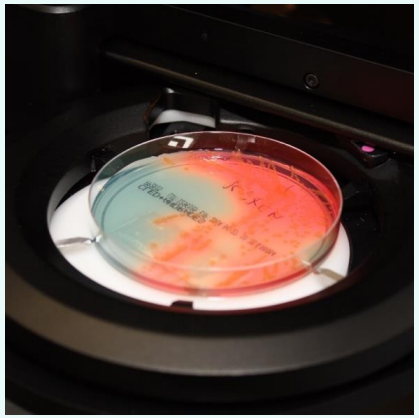
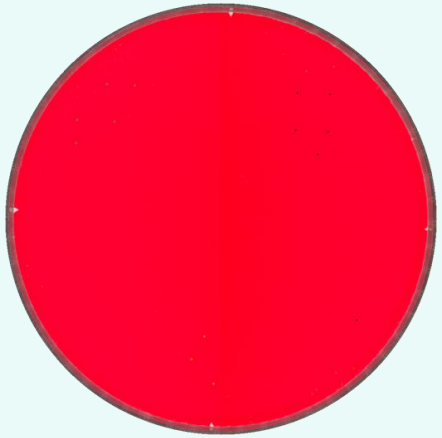
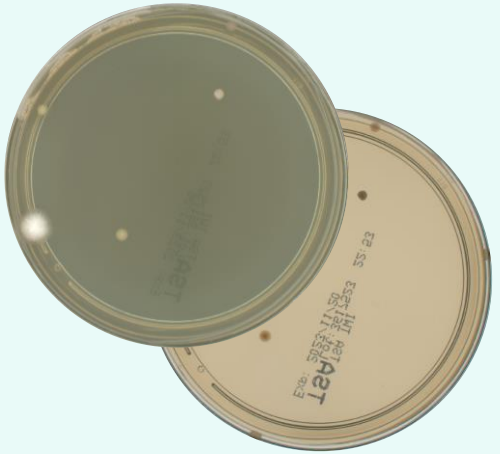


Plate handling to minimise interference

Daily and per image colour check



System check



Result:

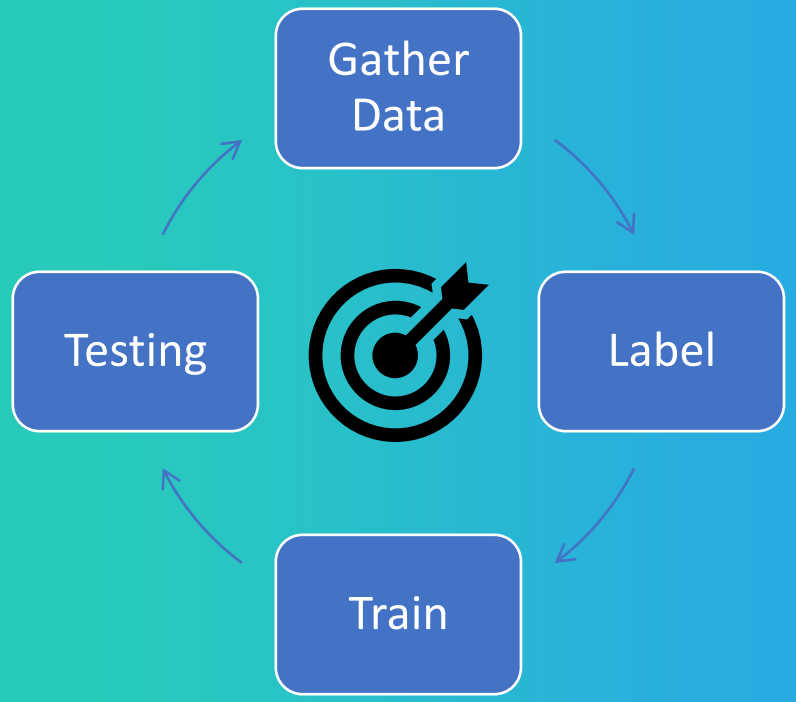
High-quality reproducible images

APAS PharmaQC - Algorithm development

Daily interaction across the development team is the key
- Cross-functional development team: Microbiology, AI, Software, Engineers, Quality
- Microbiology and AI work closely to solve issues and review data

Broad range of data built into the development program to create generalisable model
- Plates sourced globally: EU, US, AU
- Broad range of interferences, test conditions built into development (e.g. incubation times, microbiology lab practices)

Seemingly innocuous tasks and concepts often end up needing months of detailed assessment and work
- Iterative development process
- Staged design reviews to monitor algorithm development
- Pass / Fail criteria to ensure performance targets are met
- Formal performance testing to validate system

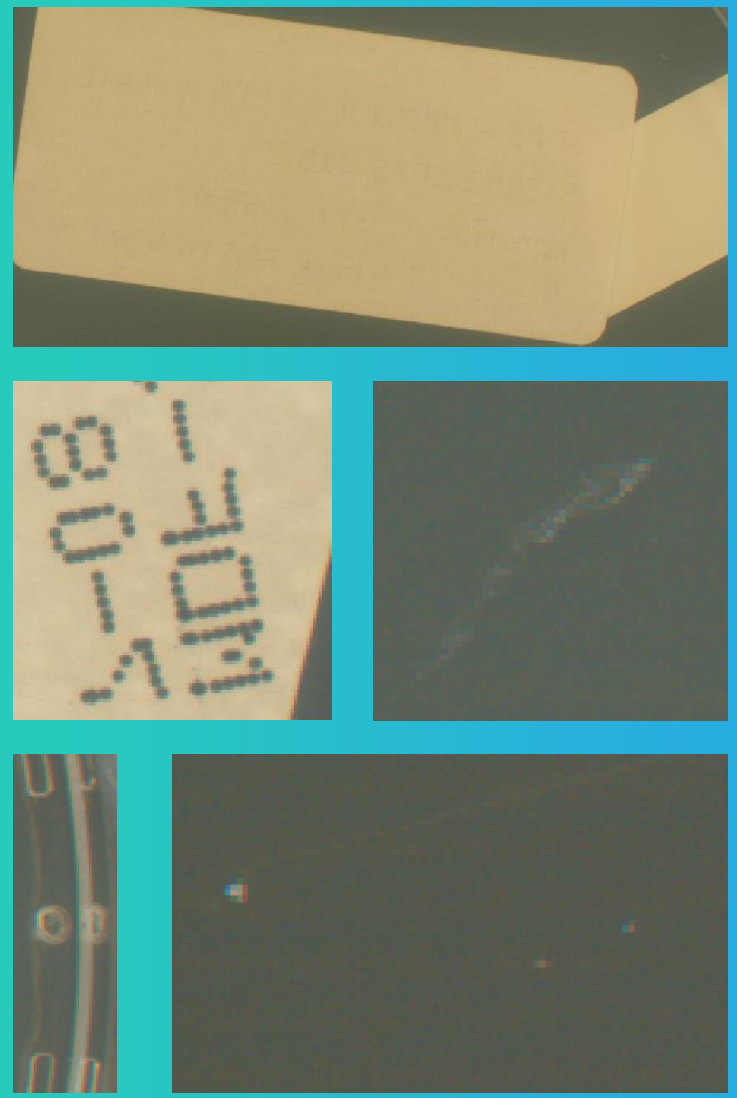


Accounting for plate interferences

Result: A generalisable AI model developed for all laboratories

A broad range of interferences are built into algorithm development to produce a robust model

- Manufacturer plate markings – dot matrices, injection moulds
- Production processes – text markings, labels applied to plates
- Agar defects – scratches, precipitate in agar
- Real-world data – Plates collected from cleanrooms



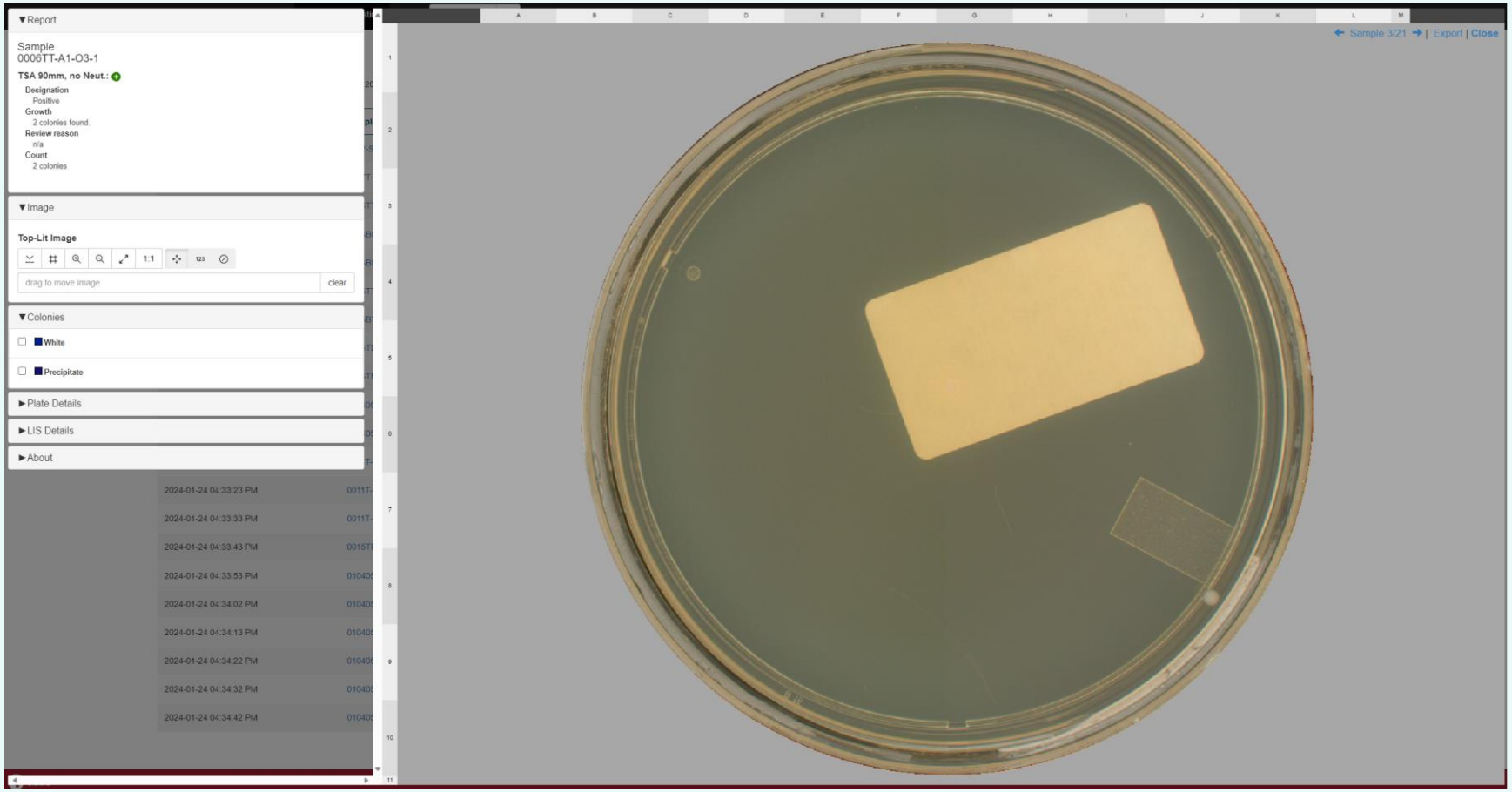
APAS PharmaQC Validation Approach

Primary validation of APAS PharmaQC as an alternative microbiological method:

- Comparison of APAS PharmaQC results to existing method (i.e. manual plate reading)
- Validation approach informed by using USP<1223>, Ph Eur 5.1.6, USP<61>, Ph Eur 2.6.12

USP<1223> validation parameters by type of microbiological test	Qualitative Test [Growth / No Growth]	Quantitative Test [Counting]	Included in Primary Validation?
Accuracy	No	Yes	Yes
Precision	No	Yes	Yes
Specificity	Yes	Yes	Partially
Limit of Detection	Yes	Yes	Yes
Limit of Quantification	No	Yes	Not applicable
Linearity	No	Yes	Yes
Operational (dynamic) range	No	Yes	Yes
Robustness (of method)	Yes	Yes	Yes
Robustness (of perimeter detection)	N/A	N/A	Added for APAS
Repeatability	Yes	Yes	See Precision
Ruggedness	Yes	Yes	Yes
Equivalency	Yes	Yes	Secondary Val.

Primary goal: Reliable colony detection

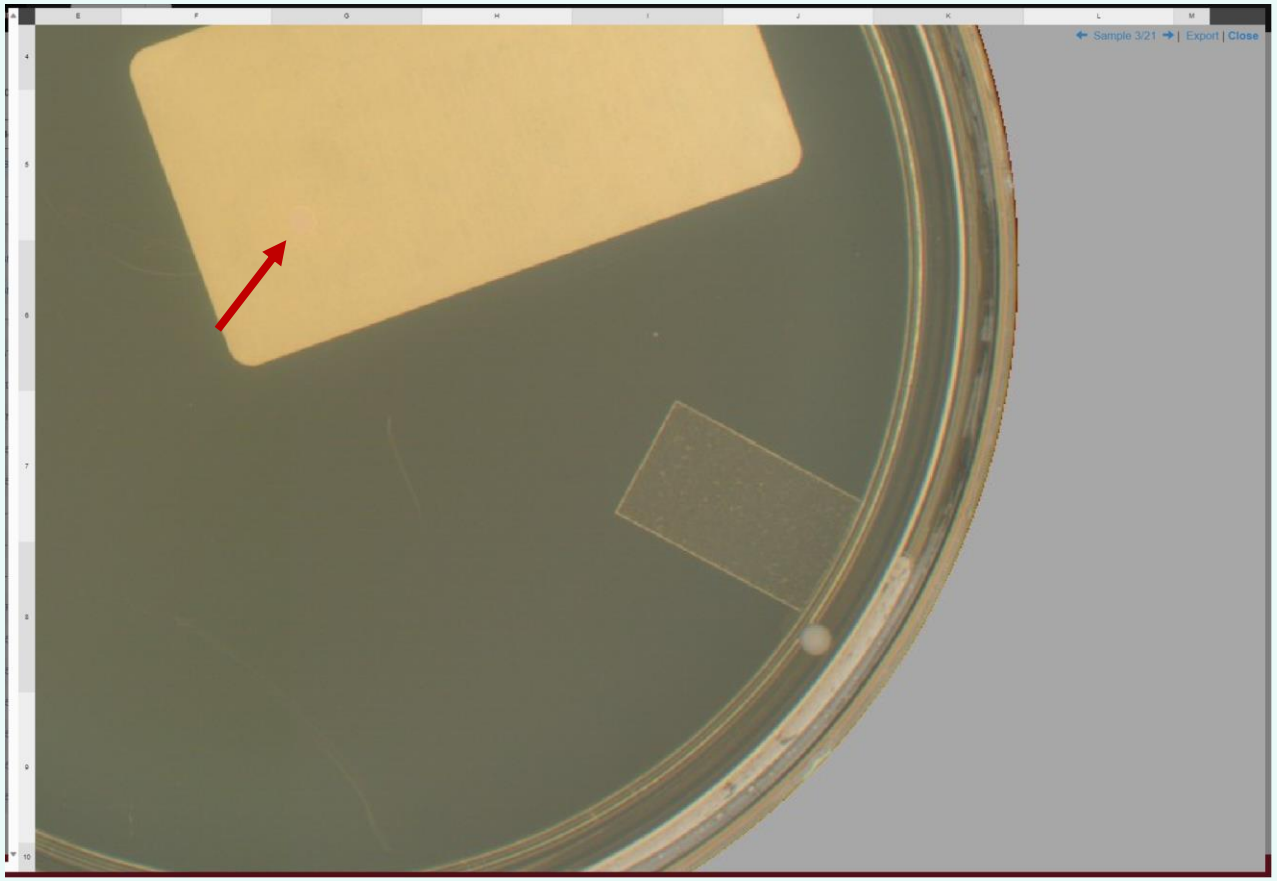


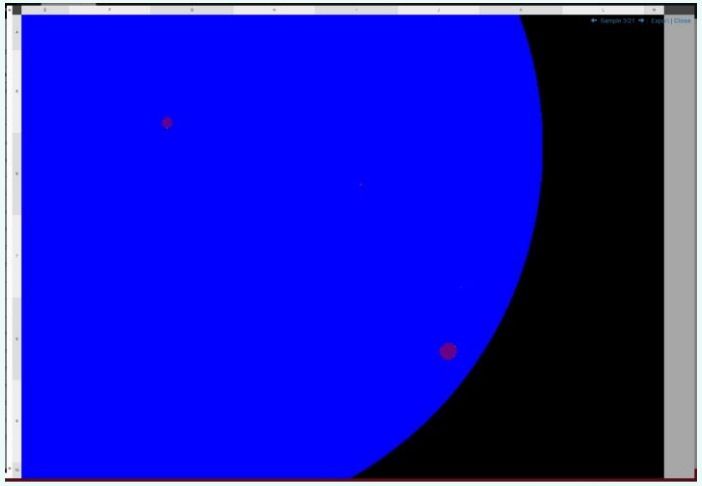
How many colonies do you see?

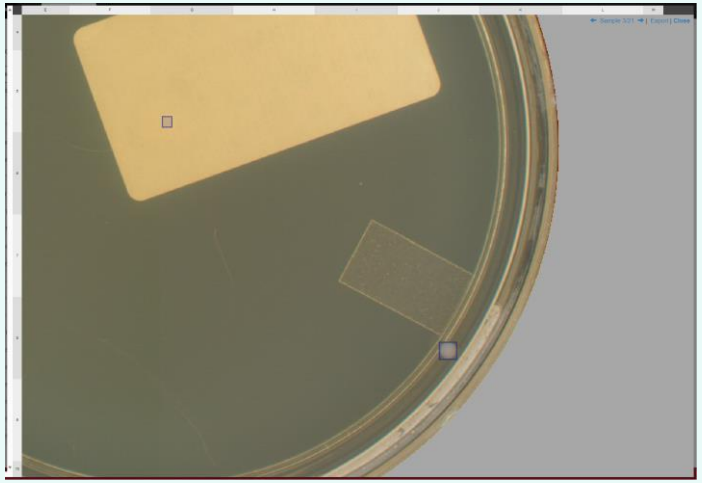
APAS: 2 colonies detected

- One edge colony
- One label colony

Reliable colony detection

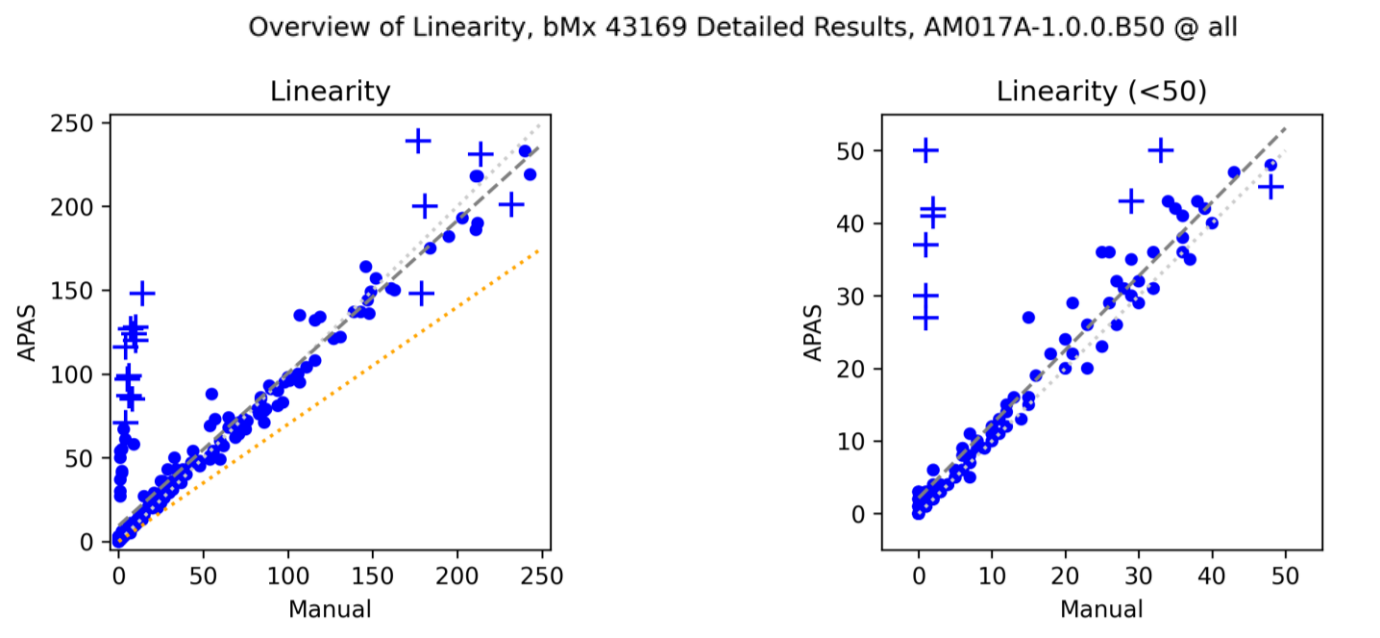






Colony counting – Preliminary Linearity data

Performance assessed across 9 organisms (including moulds), CFU range: 0-250 colonies



Example of CFU overcounting:

- Conservative design
- Mould's / spreading organisms separated for secondary review

Our Mission

Disrupt microbiology culture plate reading

Thank you !

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AstraZeneca development and validation considerations

Ben Pickard/Andrew Gravett

Why are AstraZeneca interested?

- Up to 30,000 EM agar plates are read manually and verified every month at large AZ sites
- Annual EM data from aseptic manufacturing facilities shows that >98% of plates are negative
- Occasionally humans make mistakes
- Resolves data integrity challenges

Data needed to develop the Machine Learning

Data Collection

- >8000 plates read by the reader.
- Duplicate read in normal way.
- Images analysed and algorithm developed

Colony variability

- Fungal isolates
- Coloured isolates
- Multi coloured isolates
- Swarming colonies
- Bacillus species

Plate variability

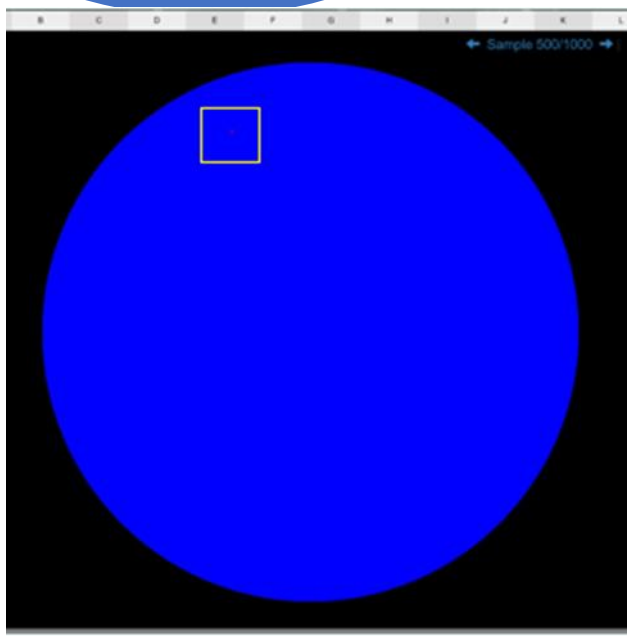
- Different media suppliers.
- Different labelling
- Different bar-coding methods

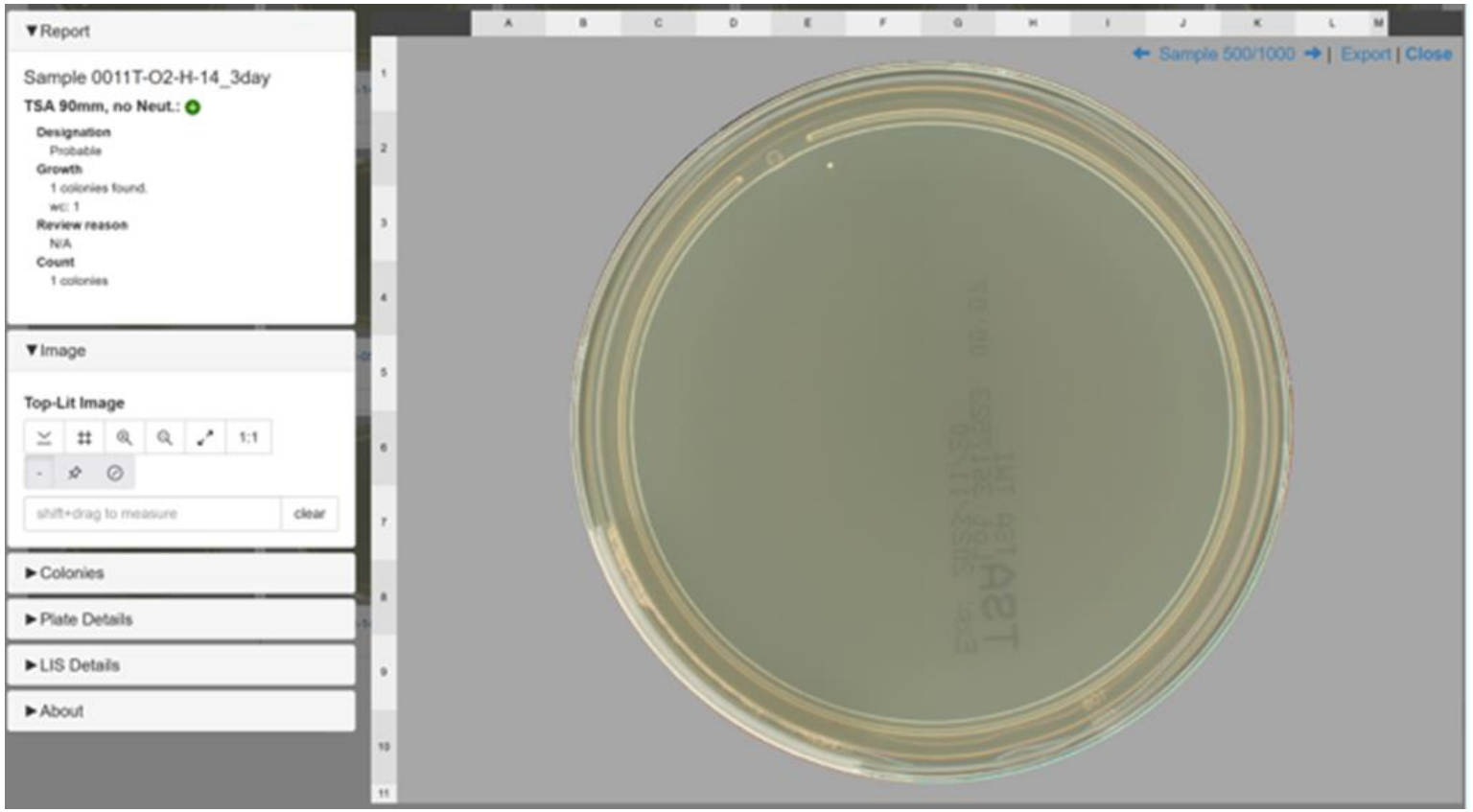
Count variability

- Inherent variability in manual counting

Key Learning Points

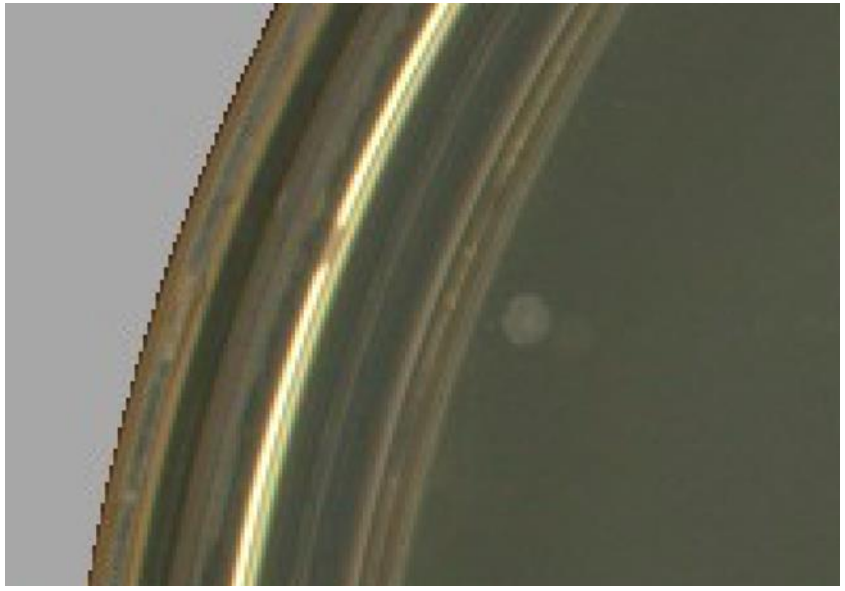
- APAS primary function is to sort ‘Growth’ from ‘No Growth’
- Remember, over 98% of plates are zero cfu (AZ facility)
- The difference between 0 and 1 is massive in Grade A, the difference between 15 and 19 is negligible.
- Single colony detection the most important factor.

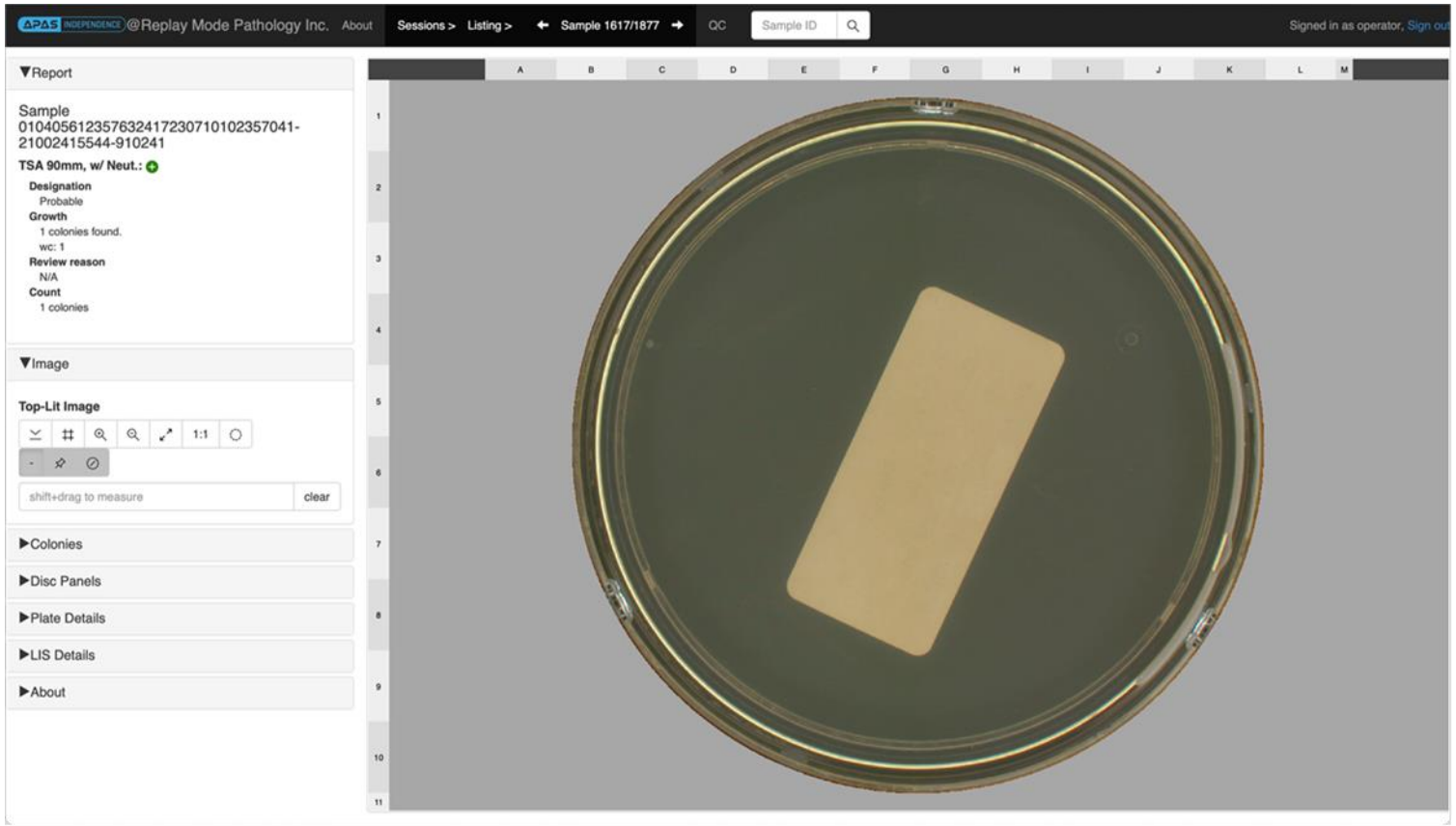




Key Learning Points

- Value of APAS proven during data collection
- Single colony missed by humans, detected by APAS
- Most important acceptance criteria are that it never misses a positive plate, and doesn't give too many false positives





▼Report

Sample 0017T-31-09

TSA 90mm, no Neut.:

Designation
Probable

Growth
2 colonies found.

Review reason
N/A

Count
2 colonies

▼Image

Top-Lit Image

1:1

drag to move image | clear

▼Colonies

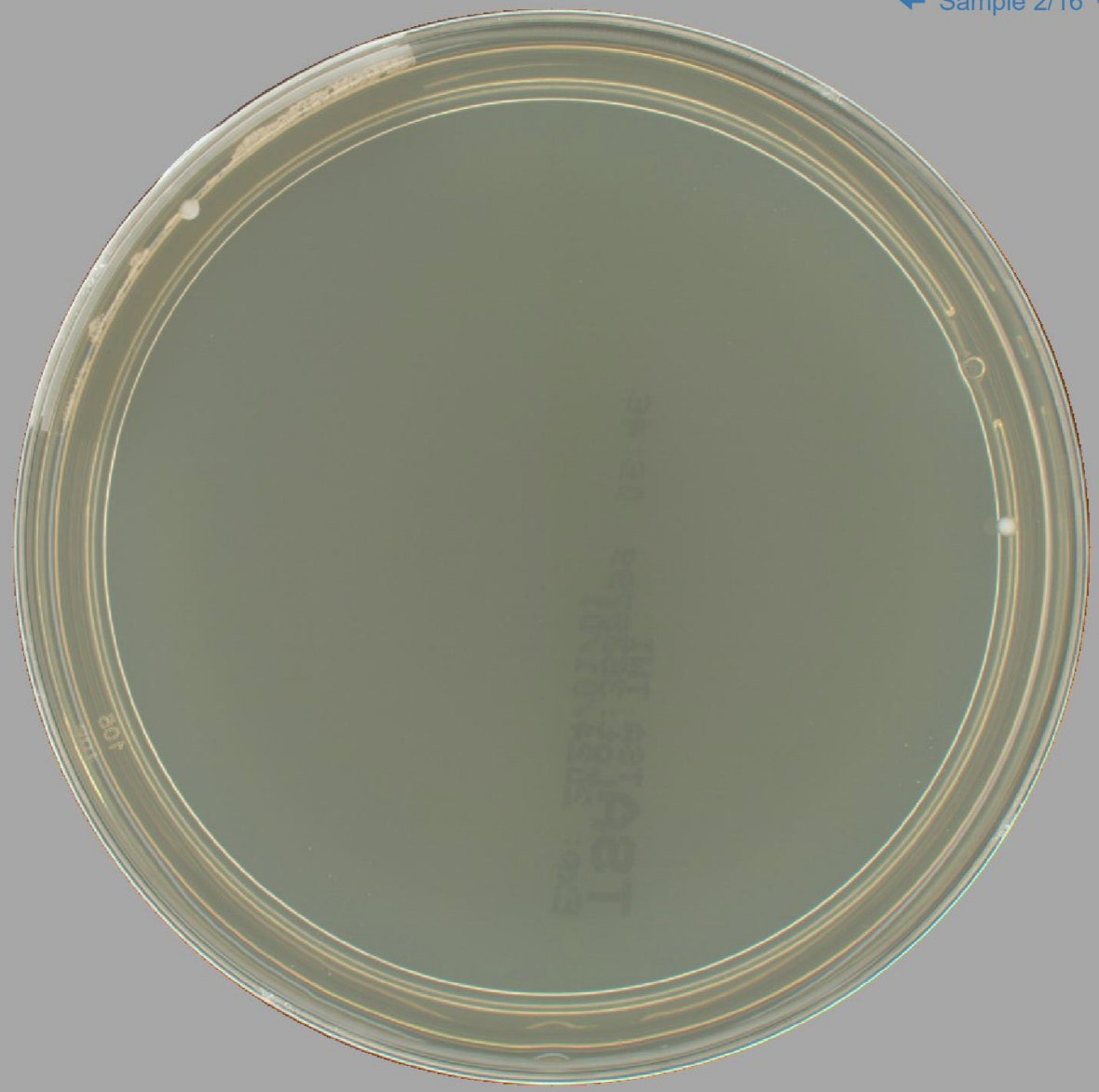
wc

▶Plate Details

▶LIS Details

▶About

Sample 2/16 | Export | **Close**



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Sample 2/16 | Export | **Close**

Proposed Secondary Validation Study

Two Stage Approach

1st Stage:

- Positive plates would be ‘contrived’ by exposing plates in general labs and interspersed with large enough number of negative plates to keep the humans ‘reading’ in representative manner.
- 710 positive plates is the target for achieving the desired sensitivity

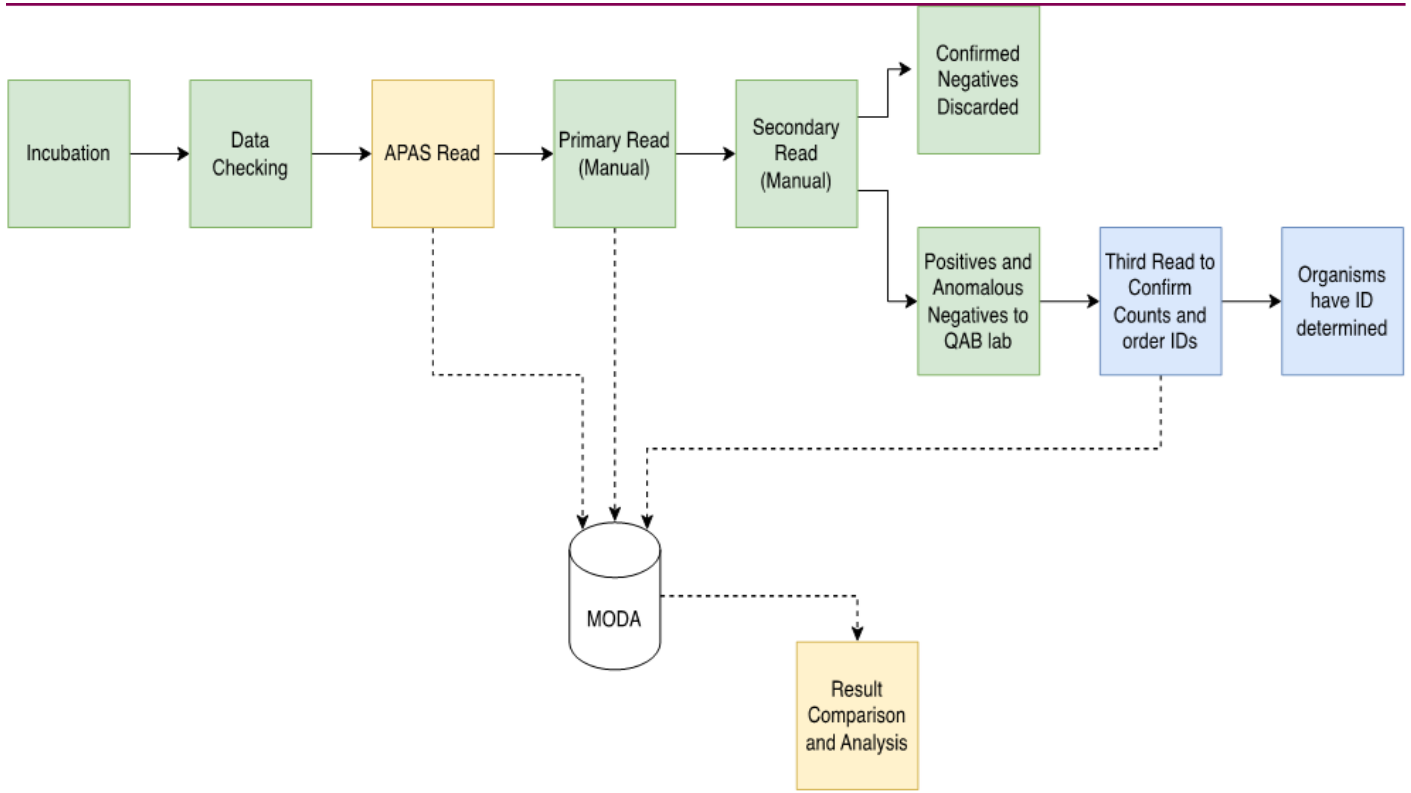
Sensitivity Target	Lower 95% Confidence Interval Target	True APAS Sensitivity	Required Positive Plates	Allowed # positive plates to be declared negative by APAS
98.0%	96.0%	99.0%	360	7
98.0%	96.0%	99.5%	190	3
98.5%	97.0%	99.5%	300	4
99.0%	98.0%	99.5%	710	7

Proposed Secondary Validation Study

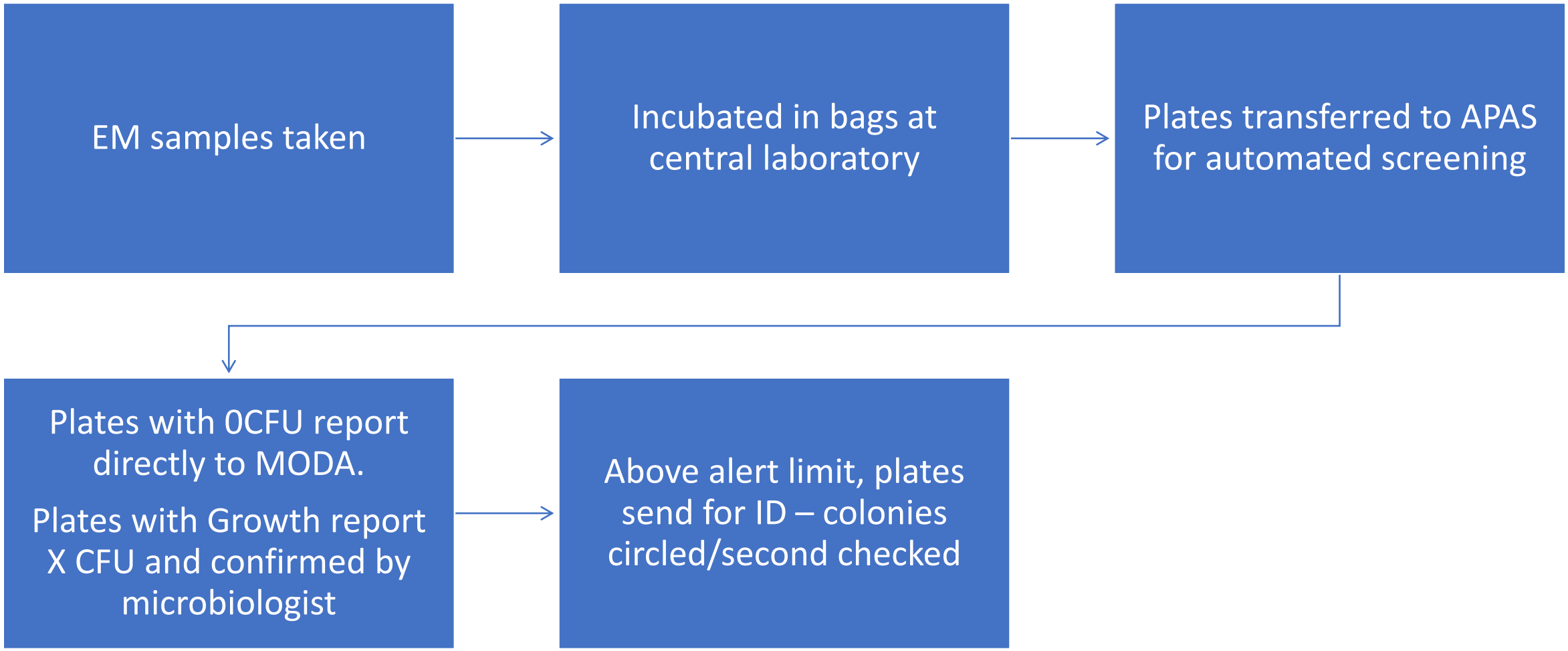
2. Establish in-use performance

2nd Stage:

- APAS instrument used as primary reader for real EM plates.
- ALL plates checked by humans and results corrected where necessary



Envisaged Future State



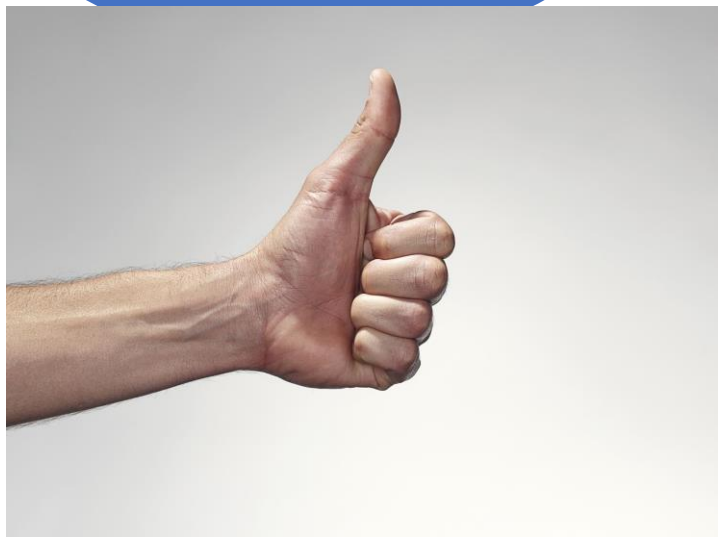
Key Points for Regulatory Opinion

- **Image Storage**
  - Manual process plates are discarded, and the raw data is the count.
  - Other plate readers approved for use have no image storage capability.
  - Sustainability and software speed challenges with storing 30,000 a month.
  - Proposal is to store validation images.
  - In process images until authorisation of results in MODA.
- **Guidance on the need to second check the negative plates.**
- **Once the model is “locked” and no longer learning. Follow normal laboratory change control GMP processes.**
  - Software updates could either be compared against the original validation images or a set of plates with counts prepared and read before software update and then immediately after and results compared.
  - Are there specific expectations for validation for the AI algorithm even though it will be locked down?

Key Points for Regulatory Opinion

- Once validated, and because there is a secure audit trail and traceable data transfer from APAS to MODA, there will be enough evidence to minimise any requirement or expectation for second checks and /or verification of negative counts?
- What is the specific minimum expectation to define equivalent or better since there is some subjectivity in counting by humans?

Potential Risks and future considerations



- Acceptance by regulators?
- Considerations for image retention
- Flawless interface with MODA
- Requirement to expand to 55mm contact plates
- Number of false positives needs to be acceptable
- On-going Performance Monitoring of APAS
- Consideration for number of ‘checks’ – percentage of negatives reviewed?
- ‘Reading’ ability of humans needs to be retained

- We see all these as important but solvable and the benefits far exceed the risks.