Responsible AI development of alternative microbiological methods used in EM – a case study with the APAS Independence

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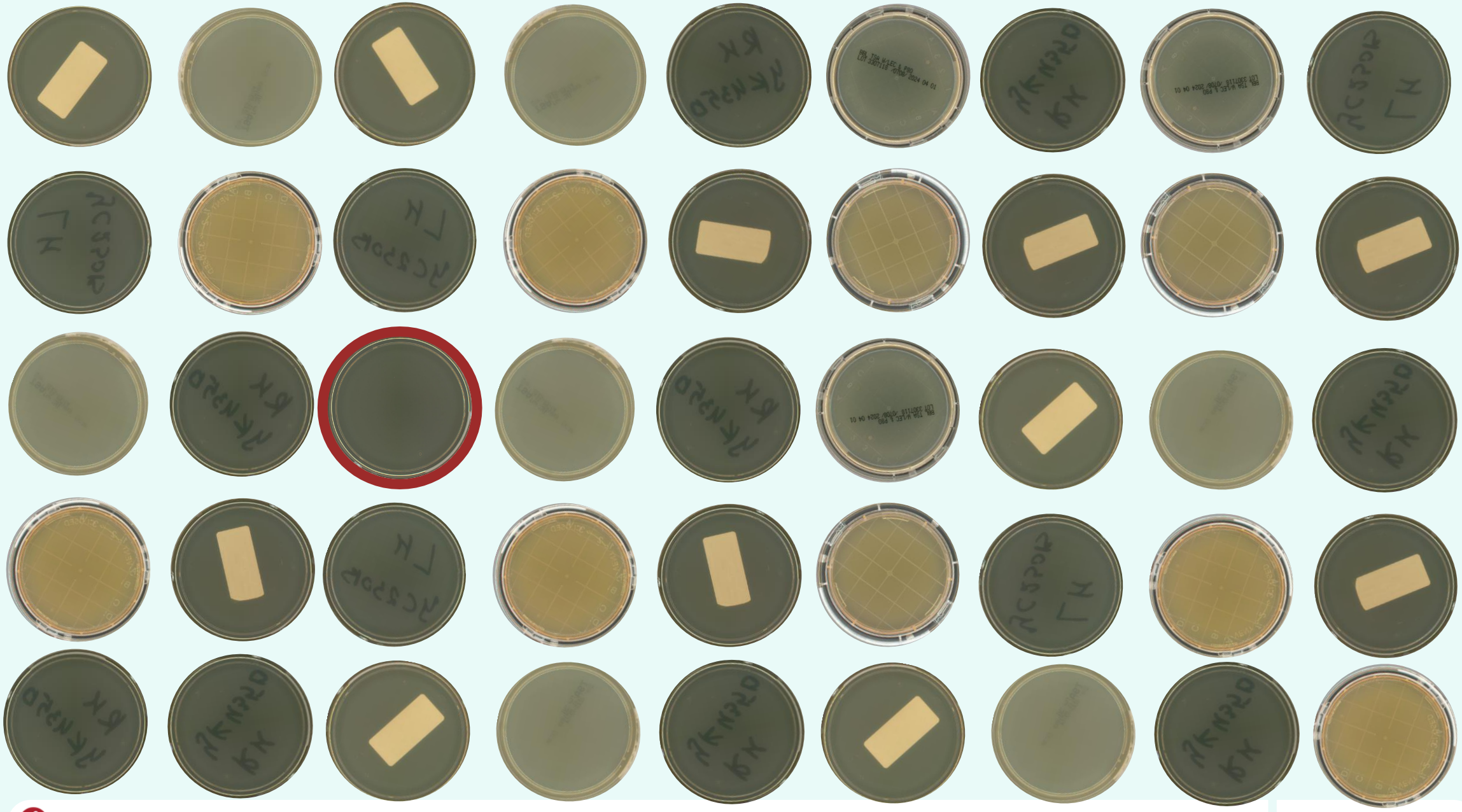
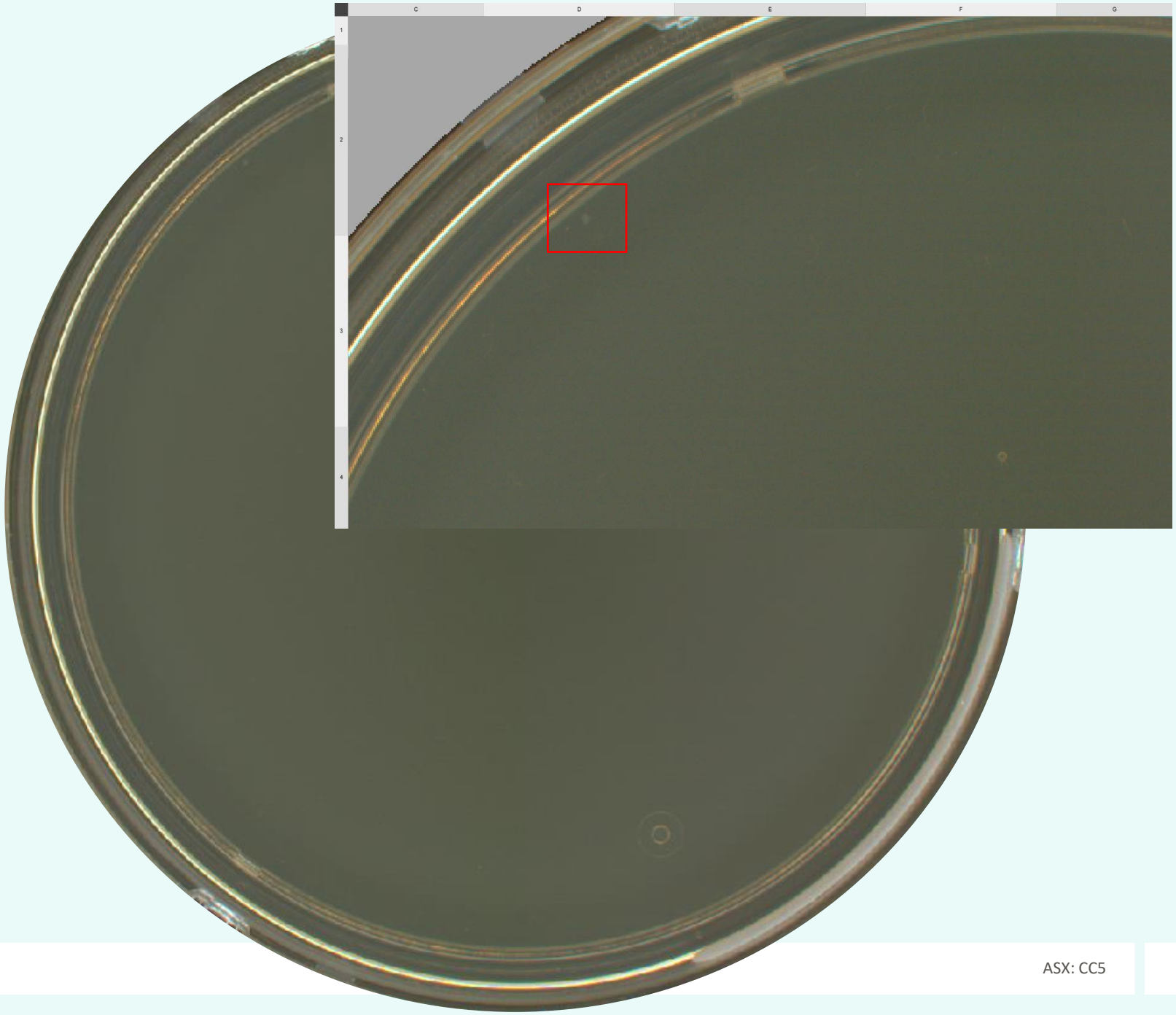
CLEVER CULTURE SYSTEMS

Problem in Micro QC

How many colonies on this plate?

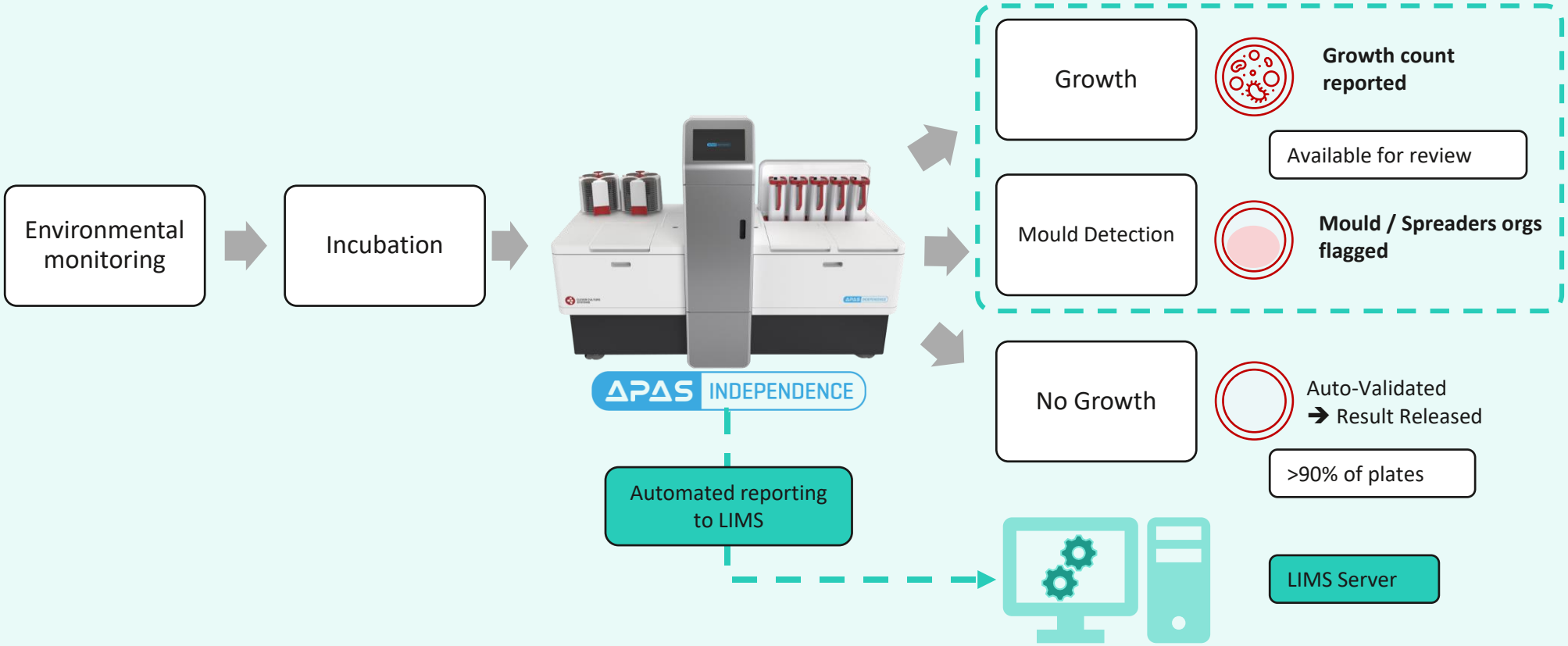




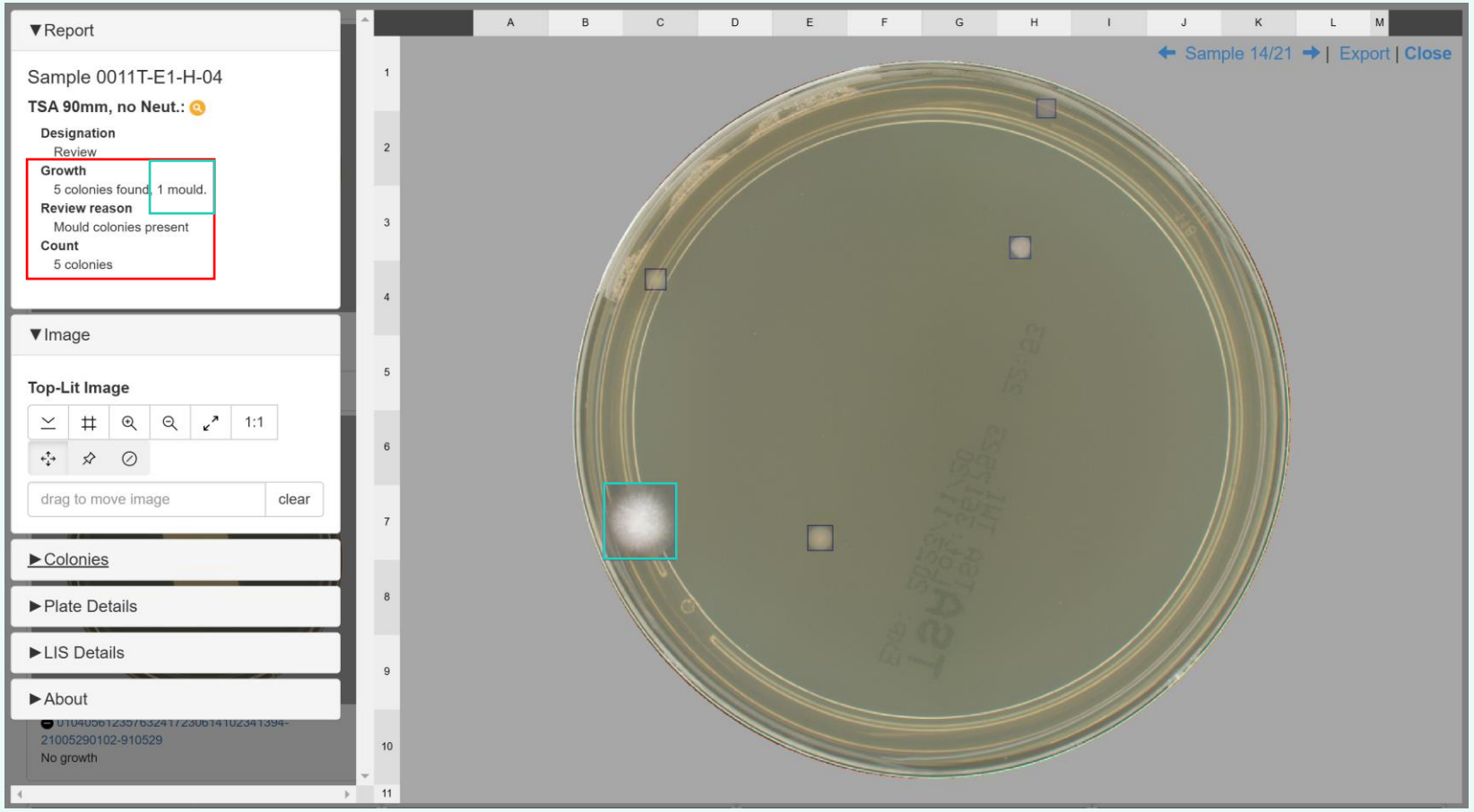
APAS Independence Operations overview

Ensures quality and data integrity of the culture plate reading workflow

Increased monitoring frequency with increased focus on EM results – Annex 1 driven



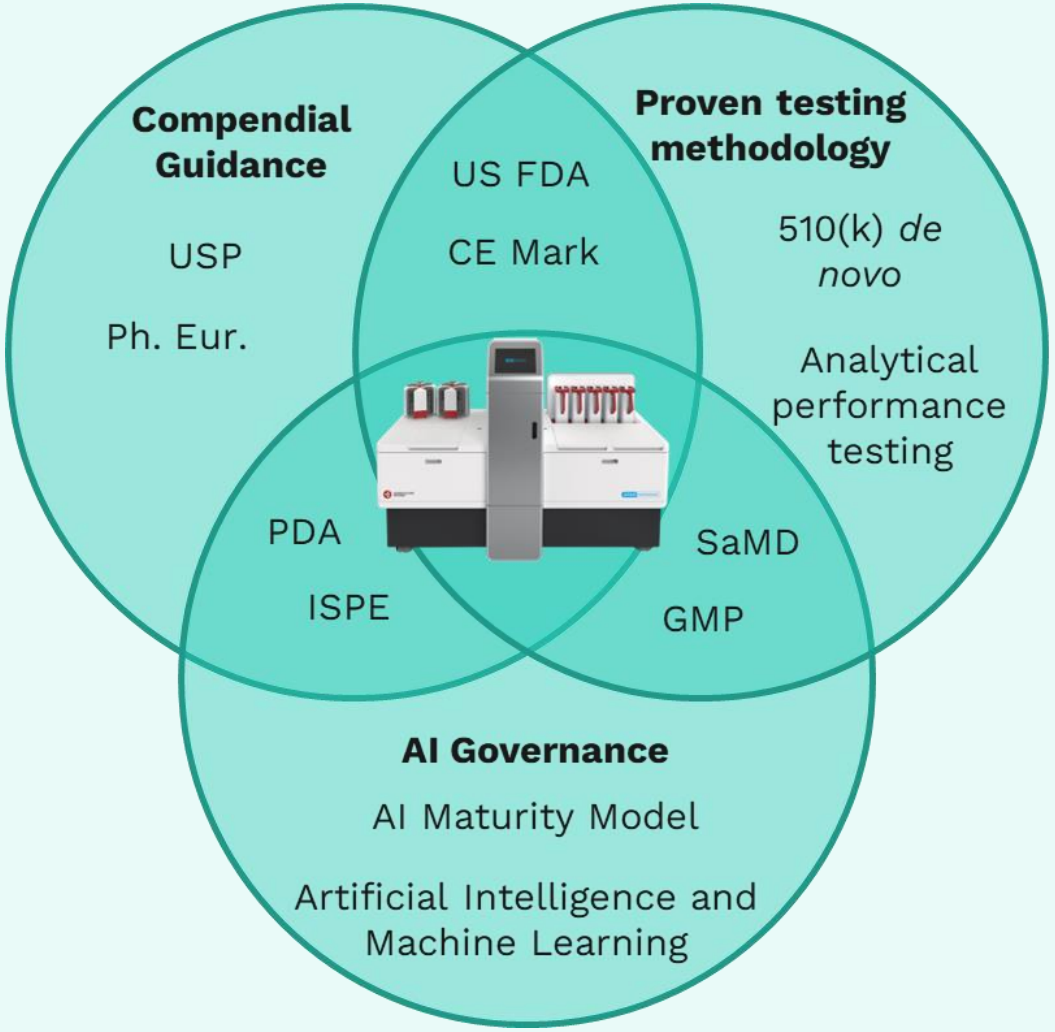
Example: AI interpretation of environmental monitoring culture plate



- ✓ High quality images available for review and storage
- ✓ Bacterial and Mould growth reported separately
- ✓ AI generated bounding boxes highlight growth on image
- ✓ Images and all data can be exported and backed up
- ✓ LIMS integration e.g. MODA, PDF reports, audit trails

Clever Culture Systems Expertise in Artificial Intelligence

- AI-technology company with expertise in microbiology, software, engineering, regulatory, quality, service and support,
- APAS - The first FDA-cleared device for microbiology plate reading
- Highly developed methodology for AI testing and validation
- Accepted performance in clinical and pharmaceutical sectors



APAS and AI GMP regulatory evolution

2016 UTI

2021 MRSA

2024 EM90

2025 EM55

2010 | 2016 | 2019 | 2021 | 2022 | 2024 | 2025

FDA CleverCS Consultation

FDA *de novo*

FDA APAS Independence

2021
- FDA AI Action plan
- ANSI
- GMLP
- FDA
- MHRA

2022
- ISPE AI Maturity Model
- AAMI CR34971

2024
- FDA PCCP

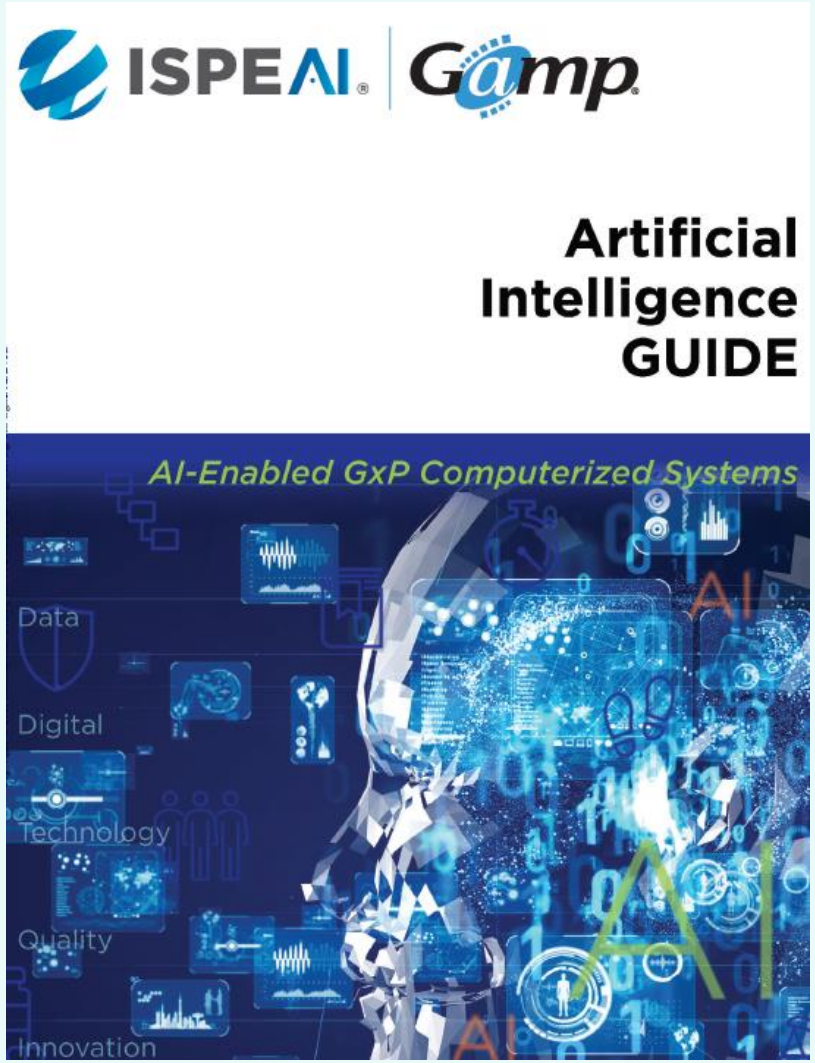
2025
- ISPE GAMP AI

18	AI/ML Devices	42	476	771

https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-enabled-medical-devices

Considerations for AI development - Pharma

- 21 CFR Part 11 – Data integrity
- EU GMP Annex 11 – Computerised Systems
- EU GMP Annex 1 - Manufacturing
- EU GMP Annex 22 – AI Draft
- Primary validation requirements (EU Ph, USPs, PDA TR)
- FDA Guide Considerations for use of AI - Support for regulatory decisions (Draft – 7 step process)
- Secondary validation requirements from industry
- ISPE GAMP5 A Risk-Based Approach to Compliant GxP Computerized Systems
- ISPE GAMP AI Guide



ISPE AI Maturity framework – informs risk and controls

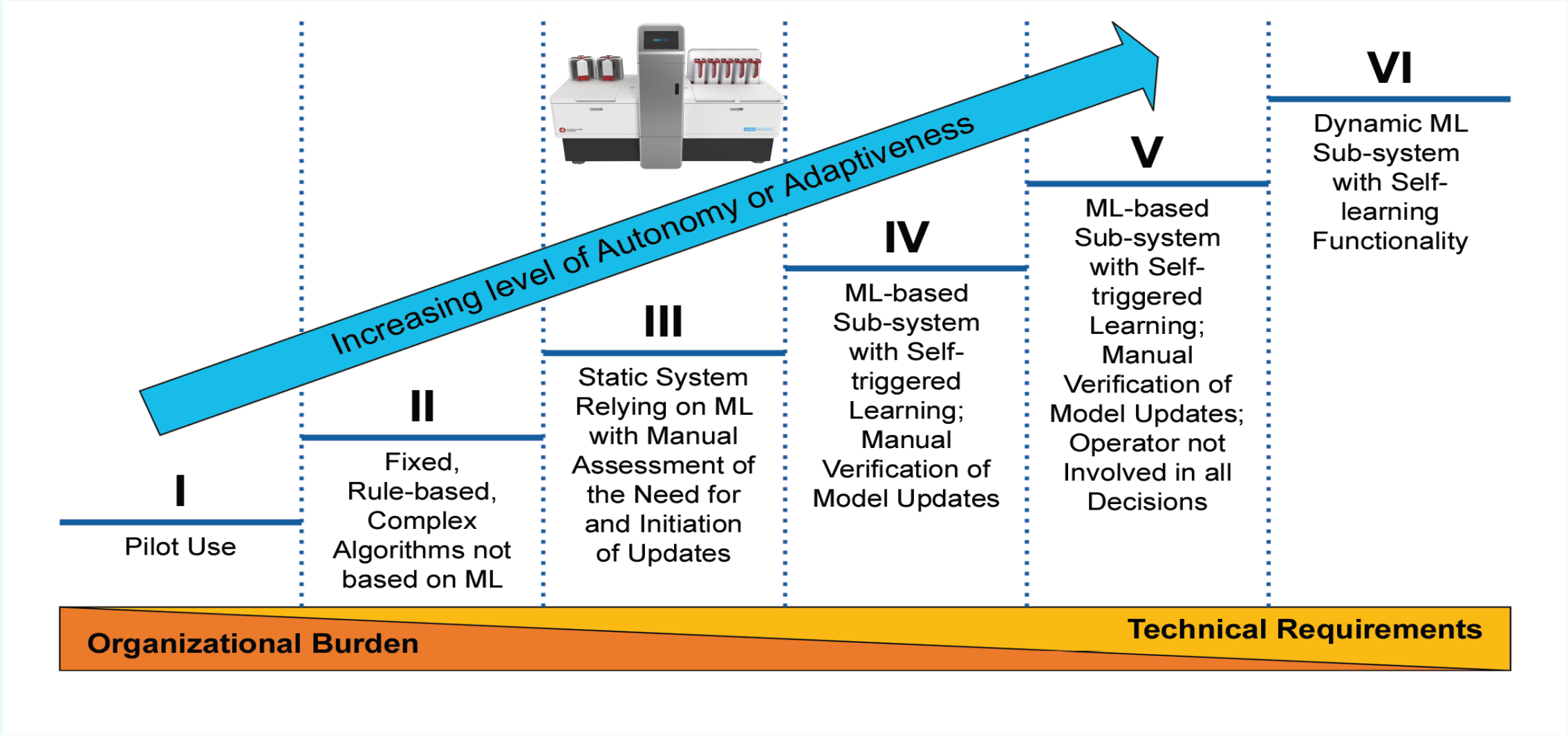


Figure taken from ISPE GAMP AI Guide, pg 216

ISPE AI Maturity Level II – Controls

- **Level II control first needs to be considered** *"Example controls for such rule-based algorithms include the selection of a data set that is fit for purpose to evaluate the performance of the rule set in a variety of scenarios in the context of use. Furthermore, acceptance testing should ensure that the algorithm is sufficiently interpretable by end users to base their decisions on the algorithm's results".*

- Examples from the vendor
  - High-level development principle and plan
    - *intended use*, media, organisms, applications
    - Data capture –user nuances, interferences,
  - Usability – beta versions to KOLs, feedback into development
  - Validation data – evaluates fit for purpose

Excerpts taken from ISPE GAMP AI Guide, pg 215-217

ISPE AI Maturity Level III – Controls

- **Level III control** *"In addition to the controls mentioned in AI Maturity Level II, further controls should be considered, such as verification of the reliability of the sourced model or training algorithms"*

- Examples of controls that have acceptance targets
  - Internal user, product, and software requirements
    - False Positive Ratio, False Negative Ratio
  - Primary validation and compliance with Pharmacopeial guidelines
- Design reviews

Verification is the *"confirmation, through the provision of objective evidence, that specified requirements have been fulfilled." ISPE GAMP5*

Excerpts taken from ISPE GAMP AI Guide, pg 215-217

Annex 22 Draft – Artificial Intelligence (Scope)

- *"This annex applies to all types of computerised systems used in the manufacturing of medicinal products and active substances, where Artificial Intelligence models are used in critical applications with direct impact on patient safety, product quality or data integrity, e.g. to predict or classify data"*
- Acceptance criteria *"4.3 No decrease"* in performance (current performance must be known)
- *The document applies to models with a deterministic output which, when given identical inputs, provide identical outputs. Models with a probabilistic output which, when given identical inputs, might not provide identical outputs are not covered by this document and should not be used in critical GMP applications.*

Bringing it all together: How is the AI generated and tested?

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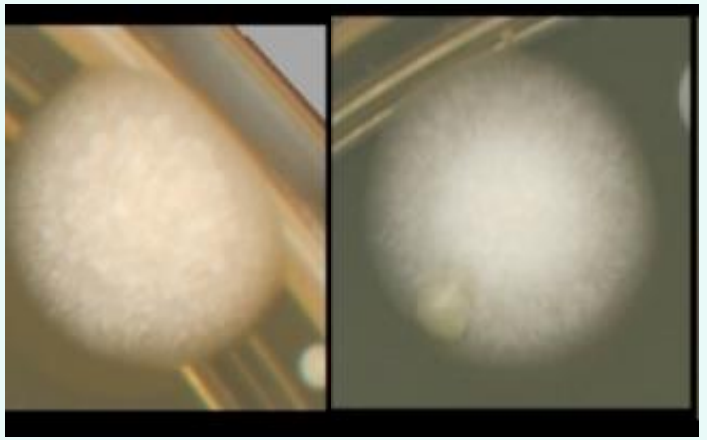
Defining what is true – the hardest part of AI!



Bacteria Mold

Defining what is true?

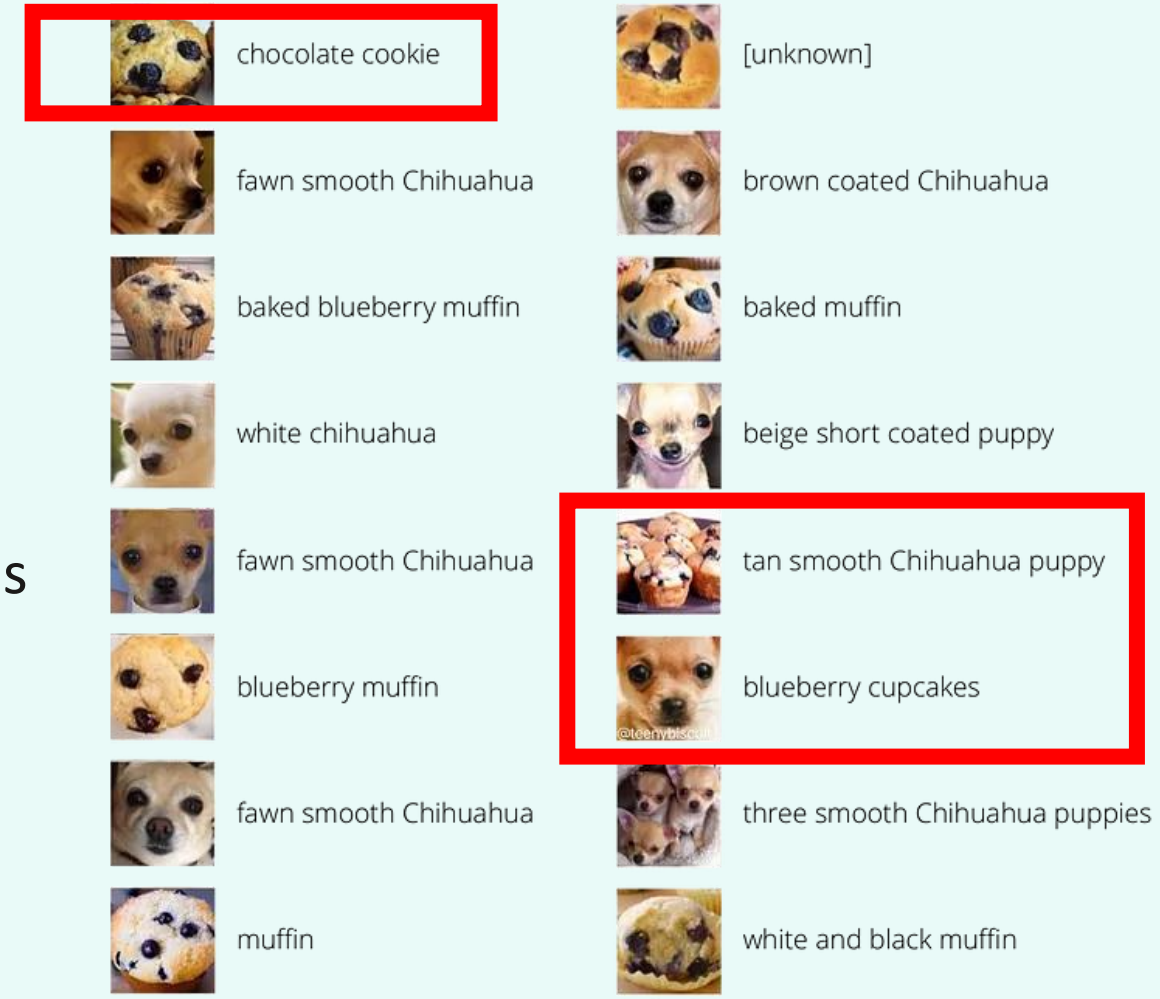
The main factor driving the quality of an AI/ML system is the input data

Important that data is representative of the real-world

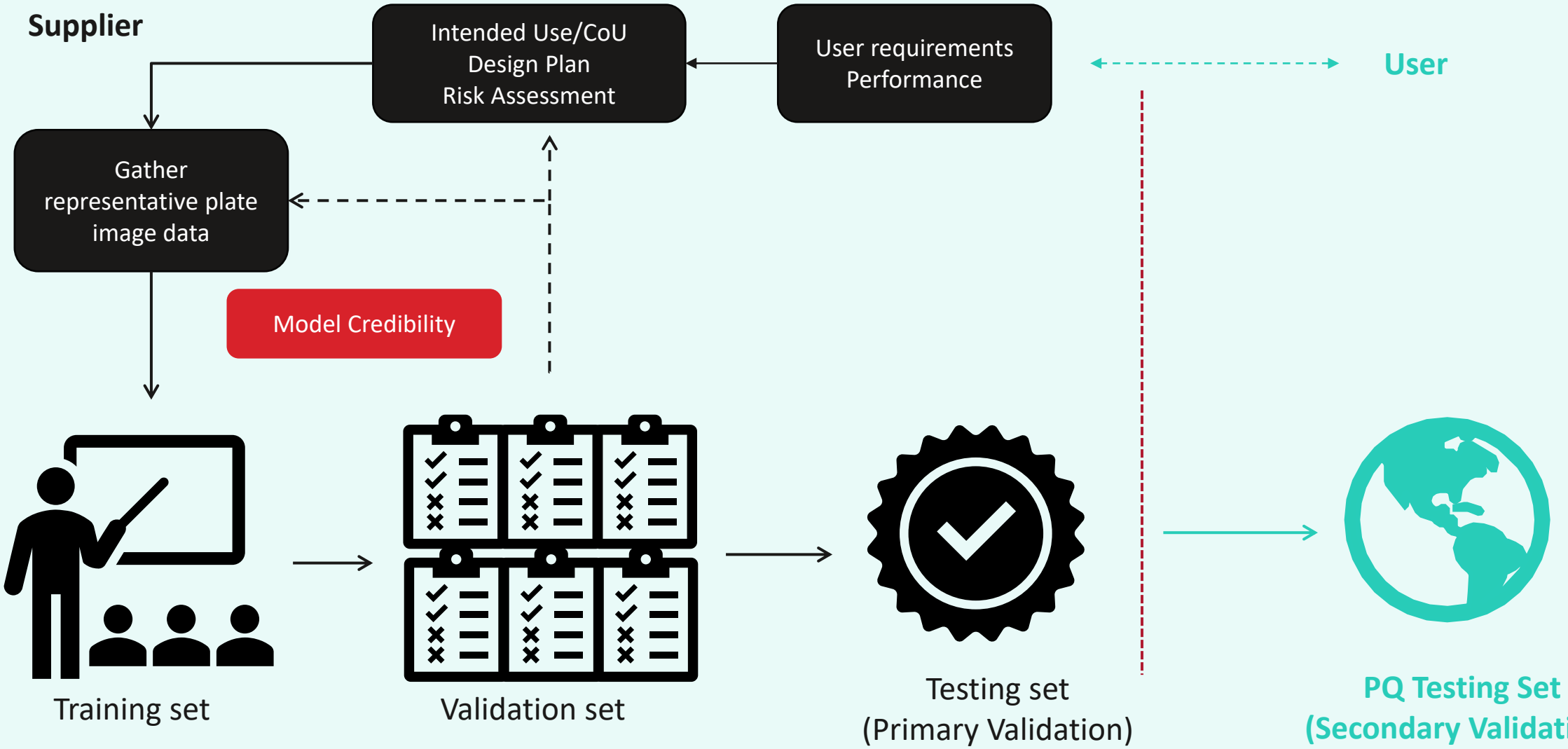
- Needs to be controlled and authentic

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

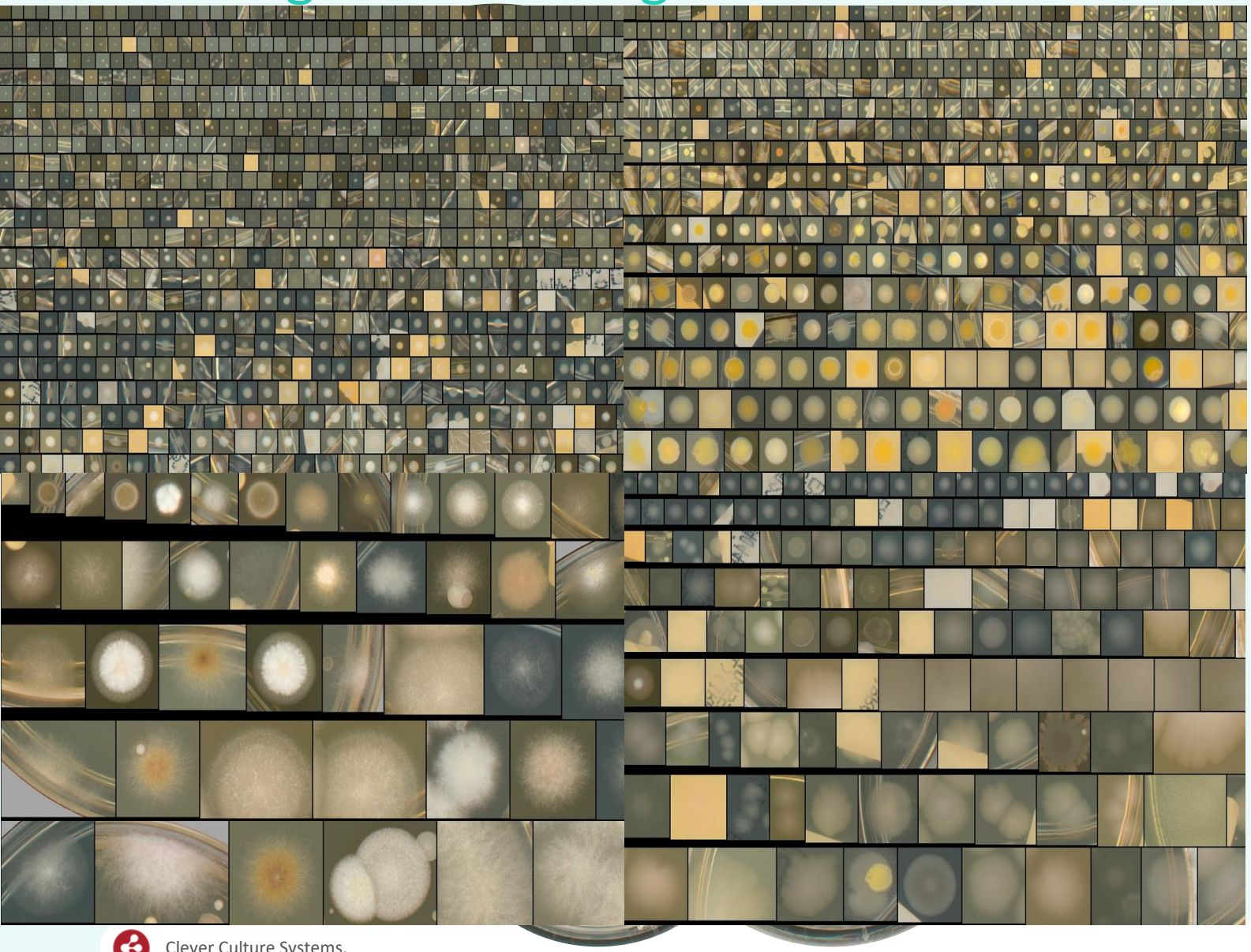
- Often don’t have in-house experts
- Data errors common in real-world
- Data cleaning is a big deal for AI companies
- CleverCS cornerstone skill is data management and integrity



Structured development and testing approach - AI lifecycle

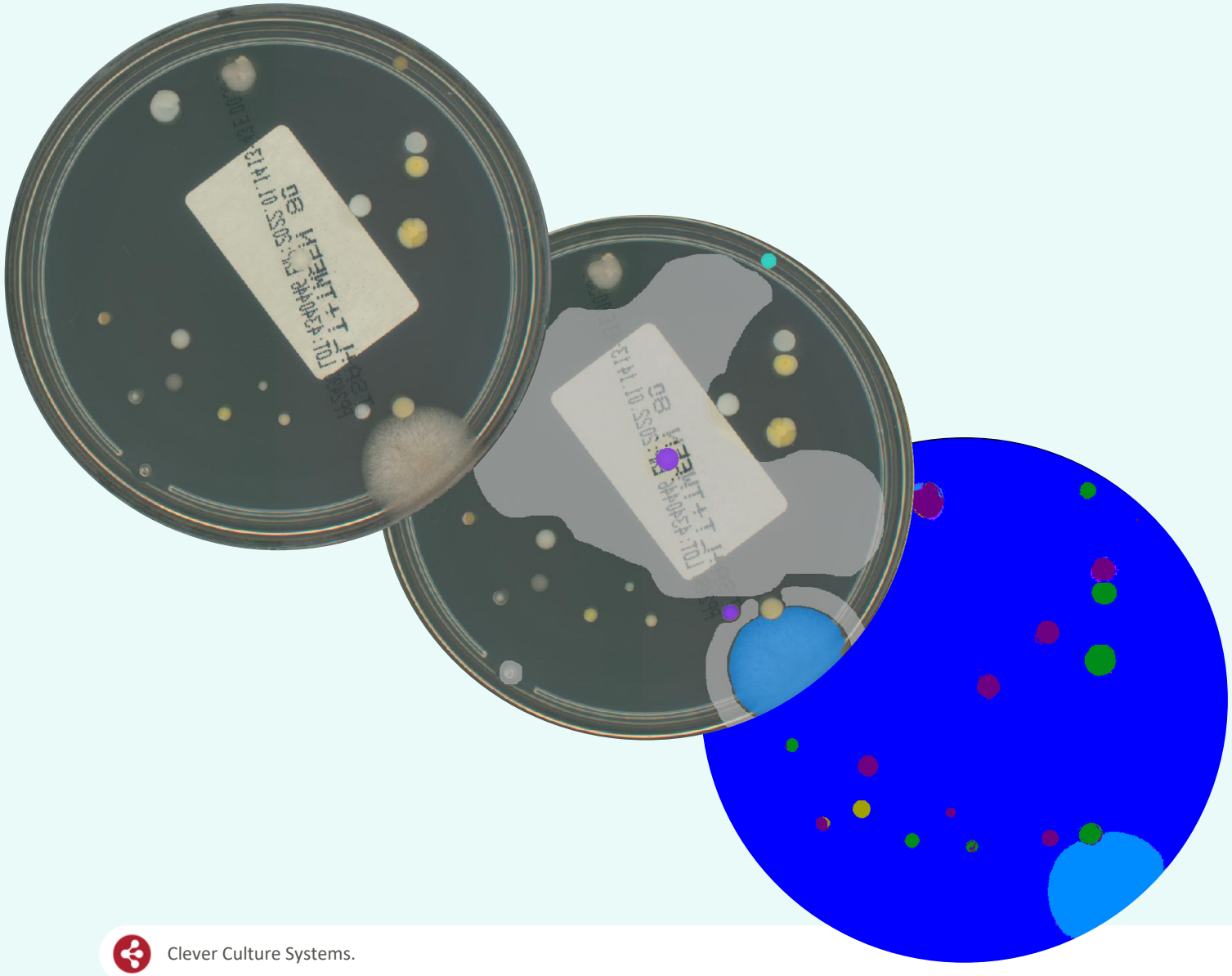


Training Data Coverage



- Training data sources are aimed to gather representative images of cleanroom environments that acts as an input to development.
- Sources:
  - Partner cleanroom facilities
  - CleverCS laboratories and peripheral environments
  - QC organisms (as recommended by media manufacturers and compendial testing methods for validation of alternative methods)
- Broad reach to reduce bias and generalise the model
- Balanced models to minimise bias

Trained for Microbiologists, by Microbiologists

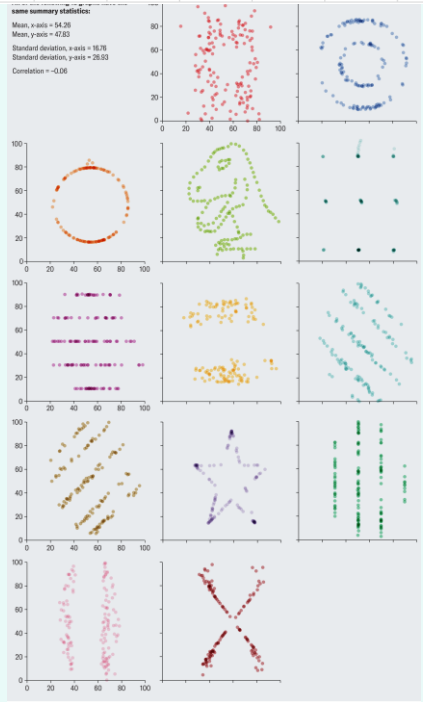


- ✓Machine learning trained by microbiologists
- ✓Colony recognition used as an input
- ✓Several cycles of iteration to improve accuracy i.e. not just a single annotation or review
- ✓Consistent analysis of each plate

Validation data sets – getting it right

- Demonstrate model progression
- Examples of datasets
  - Pilot studies for primary validation
  - Real world examples from global sites
  - Organism panels, Interference sets
- Used to monitor performance of KPIs over development iterations
- KPIs need to be fit for purpose for model and end use, e.g.
  - False negative/positive rate, Accuracy/Linearity metrics
  - Its never just one metric !
- KPIs and numbers alone do not tell the story
  - Visual assessment also drives development

		Computed Labels						
		AB	YC	WC	FF	PR	TC	Total
		■	■	■	■	■	■	Total
User Labels	AB	99.6%	0.1%	0.1%	0.1%	0.1%	0.2%	14M
	YC	3.1%	91.1%	2.6%	0.2%	0.1%	0.4%	115K
	WC	1.5%	2.1%	89.7%	4.1%	0.2%	1.1%	353K
	FF	0.7%	0.0%	0.3%	87.4%	4.1%	2.5%	289K
	PR	10.1%	0.8%	2.8%	4.4%	81.4%	0.2%	139K
	TC	0.9%	0.1%	11.9%	0.9%	0.0%	86.1%	32K
Total		14M	124K	428K	291K	130K	3.4K	
Percent Correct		99.6%	91.1%	89.7%	87.4%	81.4%	86.1%	
Computed Labels		82M	456K	2M	1M	448K	2M	



https://www.scientificamerican.com/article/what-this-graph-of-a-dinosaur-can-teach-us-about-doing-better-science/

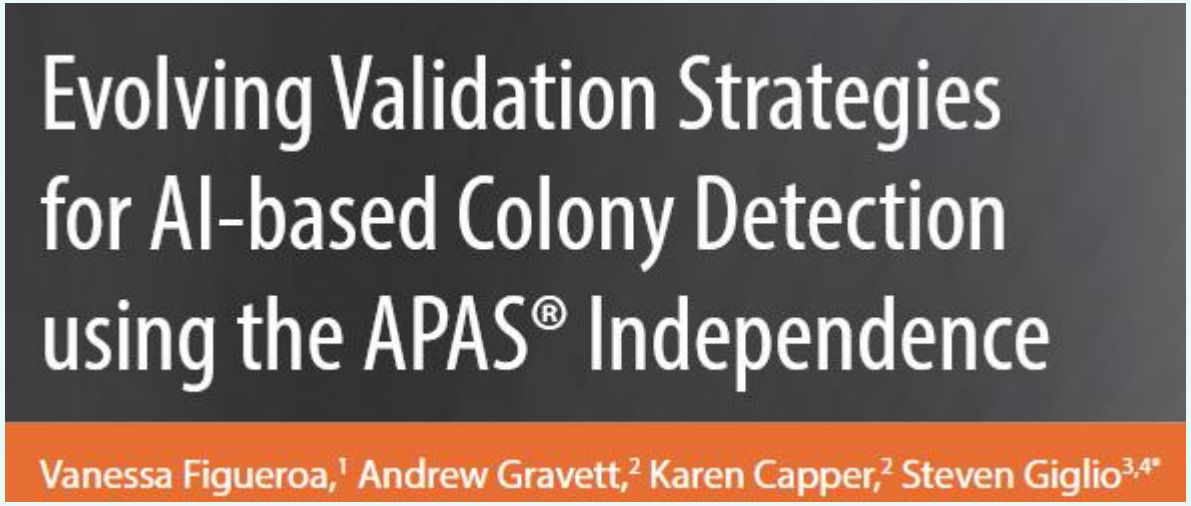
Regulatory and scientific provenance for ML design and testing - Supplier

- Primary validation performed to compendial requirements and industry expectations
- >35,000 plate images captured and assessed
- >40,000 microbiologist plate reads
- ~3,000,000 colonies counted

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	No
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	No In situ validation

Secondary validation considerations - Users

- Consider primary validation (vendor)
- Sample size estimation (e.g. by Hajian-Tilaki[1])
- Secondary validation should take into account:
  - Microbiological performance (equivalency/comparability)
  - Data integrity compliance for transfer of results to the LIS
- Establish clear procedures for discrepant analysis upfront
- Reduce biases



Vanessa Figueroa, Andrew Gravett, Karen Capper, Steven Giglio. 2024. Evolving Validation Strategies for AI-based Colony Detection using the APAS® Independence. American Pharmaceutical Review. Volume 27, Issue 5.

False negative rate target (%)	Lower 95% confidence interval target (%)	True APAS false negative rate (%)	Required positive plates (n)	Allowable # of positive plates to be declared no growth by APAS
2.0	96.0	1.0	360	7
2.0	96.0	0.5	220	5
1.5	97.0	0.5	340	5
1.0	98.0	0.5	650	7

[1]Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform. 2014 Apr;48:193-204

What could interest an auditor?

Pre Operational

- Application/Intended use is clear
- Supplier assurance on GxP computerised system requirements
- Due diligence on AI technology and governance principles for development
- Limitations are understood from risk assessments
- PMPs
- URS

Operational

- IOQ
- User documentation
- Vendor supplied data
- PQ validation plan V intended use
- Performance review
- Maintaining validated state
- Performance trending
- Residual risks and mitigations
- Data integrity of LIMS integration

Maintenance

- Plans to manage software upgrades for the algorithm
  - Global
  - Site specific
- Surveillance and feedback for updates

Conclusions

- Responsible AI development requires cross functional expertise, as does responsible AI integration activities
- Data cleanliness, management, and test execution to meet requirements is critical
- This is an evolving space
- AI-development cycles can be long, improvements will come
  - Understanding the scope of any upgrade/patch is important
  - Risk-based decisions for software upgrades
  - Managing change/upgrades internally through the change control process
- Consider automation-LIMS integration early
- Embrace and manage change with all stakeholders
  - Automation is often a catalyst for change

What does AI think a microbiologist does?

provide me a really funny cartoon with a pharmaceutical microbiologist enjoying an AI automated instrument