Case Study: Artificial Intelligence for Environmental Monitoring

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PDA Parenteral Drug Association

2023 PDA Asia Pacific Regulatory Conference

CONNECTING PEOPLE SCIENCE AND REGULATION®

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Julie Winson is the Director of Quality Assurance & Regulatory Compliance at LBT Innovations. Julie is an industry veteran, with over 40 years in the pharma and more recently medical devices sector of the life science industry. Julie has held varied roles within pharma, including analytical test development, preparing regulatory submissions and project management, quality assurance in IT, consulting in quality management systems, and finally applying all of the experience gained to product development and quality assurance of LBT Innovations' AI/ML enabled in vitro diagnostic medical device, and leads the processes required for regulatory clearance of the devices in the US and CE Marking in the EU, most recently to the IVDR.

Introduction to APAS® Independence

APAS **(Automated Plate Assessment System)** Independence,

- Is an automated plate reader that uses a camera system and machine learning model to interpret growth on microbiology culture plates and then sort.
- Is an *in vitro* diagnostic medical device, classified under 21 CFR 866.2190 Subpart C Microbiology Devices – Automated image assessment system for microbial colonies on solid culture media.

What does APAS® Independence do?

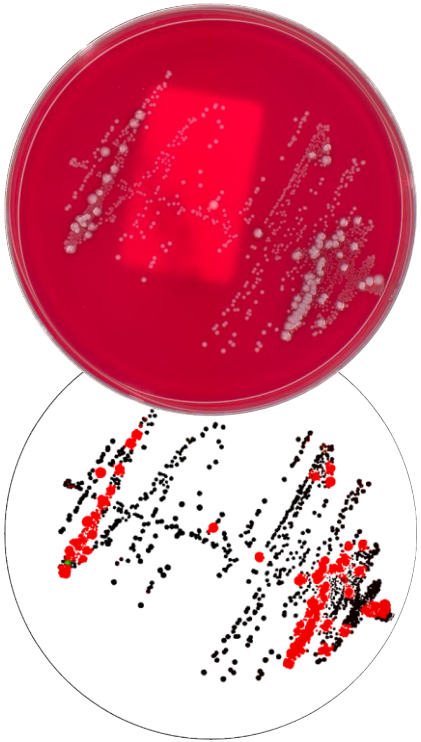
APAS separates plates with growth from those with no growth to provide efficiencies to the laboratory workflow.

- **Regulatory claim:** Plates with No Growth can be automatically reported and released without human review

APAS® Analysis Modules (AMs)

Software packages that are required by the APAS Independence instrument to perform analyses of culture plates.

- IVD device is the combination of APAS platform and analysis module
- Each AM is developed for a specific clinical indication to work with a specific media. An APAS instrument can host multiple analysis modules.
- Uses both AI/ML and traditional coding.
- Aim is to enable the instrument to 'see' what's on a culture plate as well as a microbiologist.
- Cannot be removed and installed on an alternative platform (e.g. phone, tablet)
- Once developed is 'locked' – no ability for continuous, unsupervised learning



APAS® Independence
Regulatory History in USA

2010	2013-2015	2016	2018-2020
FDA response to 513(g) request for classification – APAS treated as a different technology to current Class I colony counting devices and would require 510(k).	4 pre-submission discussions with FDA – focused mainly on the design of clinical studies, but also design of analytical performance studies.	Received marketing clearance [DEN150059] via *de novo* pathway for APAS Compact with Urine Analysis Module for screening for urinary tract infection. APAS was determined to be Class II (Special Controls).	Marketing clearance received for APAS Independence with Urine Analysis module (2018; [K183648]) and MRSA Analysis Module (2020, [K200839]) via traditional 510(k) pathway.

APAS® Independence
Regulatory History in USA

Analytical (bench) Testing

- Focus on applicability of usual tests for IVDs, as APAS is not performing an assay. Studies include Accuracy (Trueness and Precision), Limit of Detection, Limit of Blank, Analytical Specificity, Range of Assay.
  - **Maps well to Primary Validation requirements in Ph 5.1.6 Alternative Methods for Control of Microbiological Quality**

Clinical Testing

- Focus on what measures should be used for comparison (diagnostic sensitivity & specificity, PPA, NPA)
- What the reference should be (gold standard is a human, imperfect standard)
- How many samples and location/number of studies
  - **Maps well to validation of intended use and comparison with current method (Secondary Validation)**

APAS® Independence
Summary of clinical claims

	urinary tract infection	colonisation with MRSA
Decision	Screening	Screening
Patient group	General population	General population
Clinical sample and plate preparation	As instructed by plate manufacturer	As instructed by plate manufacturer
Detecting an absence of growth	Plates reported as having no growth do not require checking by a microbiologist	Plates reported as having no growth do not require checking by a microbiologist
Detecting plates with growth	All plates with growth to be reviewed by a microbiologist	BD BBL™ CHROMagar MRSA II chromogenic media – Plates reported negative for MRSA do not require checking by a microbiologist, even if other growth is present
		TFS Spectra™ MRSA chromogenic media –Plates with presumptive MRSA are sorted, but all plates with growth to be reviewed by a microbiologist
Determining amount of growth	Semi-quantitative - can provide accurate log-based enumeration of growth	Not applicable

CDRH experience with AI/ML

- See list of devices at Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices | FDA[1]
- By October 2023, there were almost 700 devices listed as AI/ML-enabled, **5 in Microbiology**.
- FDA do not claim that the list is exhaustive
  - E.g. 2 CCS MRSA devices are not listed and counted in Microbiology.
- Therefore, we assume that the CDRH branch of FDA has significant experience, but we have no experience with CDER.

Panel (Lead)	No.
Anesthesiology	6
Cardiovascular	71
Clinical Chemistry	6
Dental	1
Ear Nose & Throat	2
Gastroenterology & Urology	2
Gastroenterology/Urology	5
Gastroenterology-Urology	4
General And Plastic Surgery	5
General Hospital	3
Hematology	15
Immunology	1
Microbiology	5
Neurology	20
Obstetrics And Gynecology	1
Ophthalmic	9
Orthopedic	1
Pathology	4
Radiology	531
Grand Total	**692**

1. https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

What makes APAS® PharmaQC useful for environmental monitoring?

- Common business need:
  - Efficiency: Remove plates with no growth so that skilled resources can focus on plates with growth.
  - Ability to detect 1 colony on the plate – i.e. difference between 0 and 1.
- Additional requirements:
  - Provide an accurate total colony count when >1 cfu on the plate
  - Meet the requirements of 21 CFR Part 11

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1. PharmaLab 2023, Automated Reading of Agar Plates using AI, Andrew Gravett, AstraZeneca

Why APAS® PharmaQC?
Utilises a mature, stable technology

ISPE AI Maturity Model

Table 1: Control design stages.

Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
The system is used in parallel to the normal GxP processes	The system is executing a GxP process automatically but must be actively approved by the operator	The system is executing the process automatically but can be revised by the operator	The system is running automatically and controls itself	The system is running automatically and corrects itself

Table 2: Autonomy stages.

Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Fixed algorithms are used (No machine learning)	The system is used in a locked state. Updates are performed by manual retraining with new training data sets	Updates are performed after indication by the system with a manual retraining	Updates are performed by automated retraining with a manual verifi cation step	The system is fully automated and learns independently with a quantifi able optimization goal	The system is fully automated and selfdetermines its task competency and strategy

- By AI system maturity, ISPE means '*the extent to which an AI system can take control and evolve based on its own mechanisms, subject to the constraints imposed on the system in the form of user or regulatory requirements'*.

- Human intervention required for both Clinical and EM application
  - Control design stage 2 – 3
  - Autonomy stage 1

1. https://ispe.org/pharmaceutical-engineering/march-april-2022/ai-maturity-model-gxp-application-foundation-ai

Why APAS® PharmaQC?

Already meets stringent requirements for design control & testing

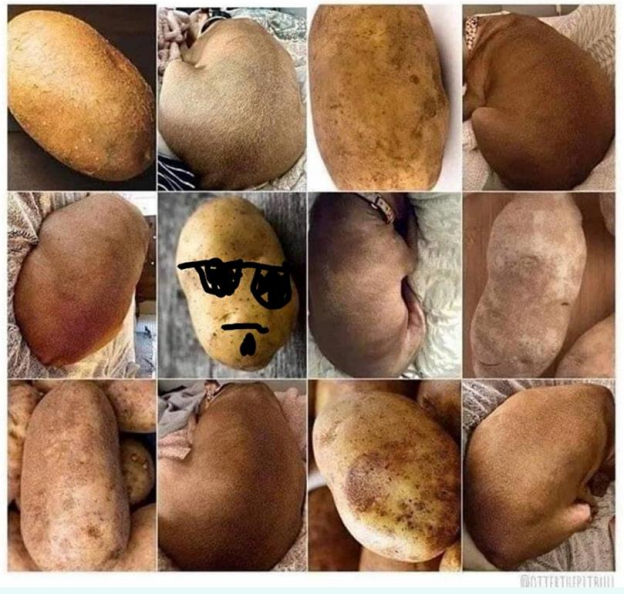
- 21 CFR Part 820 Medical Devices
- All medical device software - ISO 13485:2016, IEC 62304 (medical device software), IEC 62366-1 (human factors/usability)
- Good Machine Learning Practice (GMLP) Guiding Principles (US FDA, MHRA, Health Canada) October 2021
- AAMI Consensus Report CR34971:2023. Guidance on the application of ISO 14971 (Application of Risk Management to Medical Devices) to artificial intelligence and machine learning.
- ANSI Standardization Empowering AI-enabled Systems in Healthcare. March 2021.
- FDA – Digital Health Center of Excellence in CDRH – AL/ML Action Plan
- FDA – Marketing Submission Recommendations for a Predetermined Change Control Plan for AI/ML-enabled device Software Functions
- BS 30440:2023 – Validation framework for the use of AI in healthcare

Why APAS® PharmaQC?
Uses same method for Analysis Module Development

AI classifier development

- Analysis module includes visual imaging technology, machine learning algorithms and traditional coding.
- The AI classifier classifies every pixel within a highly controlled image of a culture plate into one of a number of defined categories.
- Supervised learning: Expert microbiolgists label images to classify specific areas within an image of a plate to train the AI classifier

Data Quality is Important



….two more ……

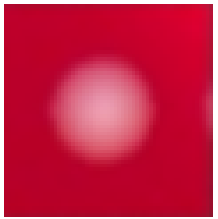
APAS® PharmaQC – Uses same method for Analysis Module Development

AI classifier development

- Must use images that are representative of 'real world' application
- Include 'challenge' images – defects in the agar, colonies obscured by labels

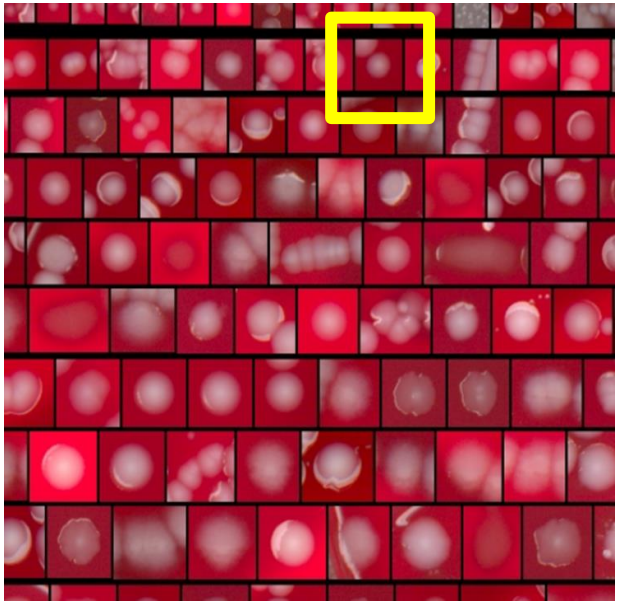
- Challenges: how much data, quality of 'truth'

Coliform group



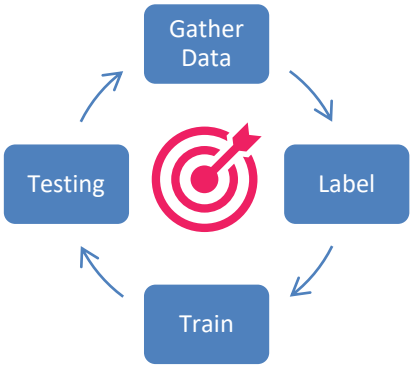
Strep group

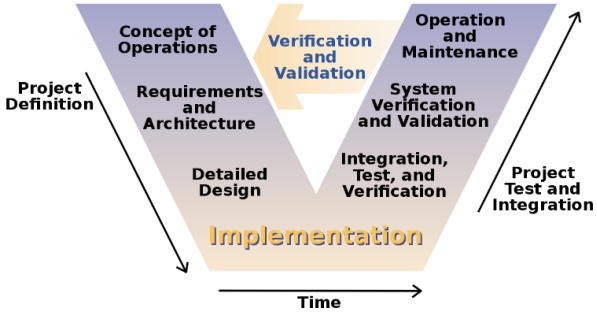
Data Quality is important



APAS® PharmaQC – Uses same method for Analysis Module Development

- Development requires close interaction between development team
  - Microbiologists
  - ML Specialists
  - Software engineers
  - Regulatory/Quality
- Challenge assumptions
- Revisit requirements
- Re-develop ML algorithm
- Pilot testing
- Formal testing - Pass/Fail





Why APAS® PharmaQC?

Minimal change to existing EM processes

Is APAS really an alternative microbiological method?

- Same sampling locations, plate preparation method, people, incubation conditions, process for dealing with plates with growth

Why APAS® PharmaQC?

Structured Validation Approach

- Good practice requires the validation datasets to be completely different to those used for training and testing.
- There are two distinct validation datasets, one used for bench and challenge testing of different aspects of the technology, and the other for demonstrating comparative performance with the current method that is being replaced.
  - Bench testing includes accuracy, precision, robustness, linearity, specificity, and can involve model systems, especially when generating challenge tests. This is called analytical performance testing for an IVD medical device and primary validation by Ph Eur 5.1.6 .
  - Secondary validation involves *in situ* comparative performance. It requires consideration of the statistical methods to be used and therefore the sample size required to achieve the required statistical accuracy. This is the equivalent of clinical testing.

Why APAS® PharmaQC?
Can be maintained in validated state

- Once developed, ML algorithms are ‘locked’ – no ability for continuous, unsupervised learning.
- Aspects of the system that do not affect or influence image interpretation (such as the robotics) can be identified and managed using current change control processes.
- Aspects that will or may affect image interpretation can also be identified – this includes some traditional code as well as ML algorithm.
- For medical devices, FDA proposes a system of predefined change control plans (PCCPs), which are agreed as part of the initial regulatory submission and are then used to manage changes to AI/ML enabled software functions.
- Similar method can be implemented for managing changes to implemented system, PCCP can include what triggers a change, how these changes are made, tested and approved before implementation and revalidation.

Validation Approach - APAS as an alternative microbiological method

Key documents that have informed the program for validation of APAS as an alternative microbiological method:

- USP<1223> Validation of Alternative Microbiological Methods,
- Ph Eur 5.1.6 Alternative Methods for Control of Microbiological Quality,
- USP<61>Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests
- Ph Eur 2.6.12 Total Viable Aerobic Count.

Primary Validation Scope

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.

Validation Approach - APAS as an alternative microbiological method

- Currently executing these tests.
- Challenge has been to establish acceptance criteria showing non-inferiority to current method.
- Therefore, once completed, will have our interpretation of meaning of test for APAS, explanation of how test was performed, measured and analysed, and the results.
- Testing will define the limitations.

- Expect that these results can be used to support the testing program developed by each customer.

Primary Validation Scope

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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 (detection of colonies at plate perimeter)	N/A	N/A	Added for APAS
Repeatability	Yes	Yes	See Precision
Ruggedness	Yes	Yes	Yes
Equivalency	Yes	Yes	Secondary Val.

AZ Experience

Key Learning Points

- Pilot primary validation study has shown difficulties in counting accurately at higher end of the count range especially with some organisms.
- However, this is also seen in humans, where differences of 20-40 colonies have been observed.
- IS THIS IMPORTANT?
- APAS would sort these plates as requiring human review.

Update : Latest software is much improved in this aspect, however in the real world all positive plates are flagged for review.

Figure 3. Example of B. spizizenii growth demonstrating variable morphology, size, and confluence

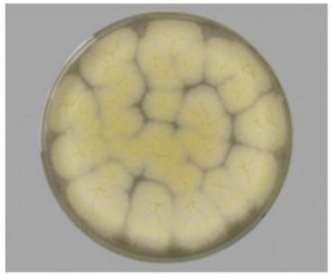

Figure 4. Example of A. brasiliensis growth changes over time demonstrating counting challenges

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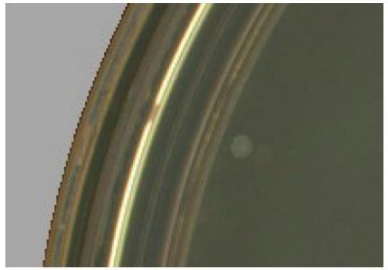
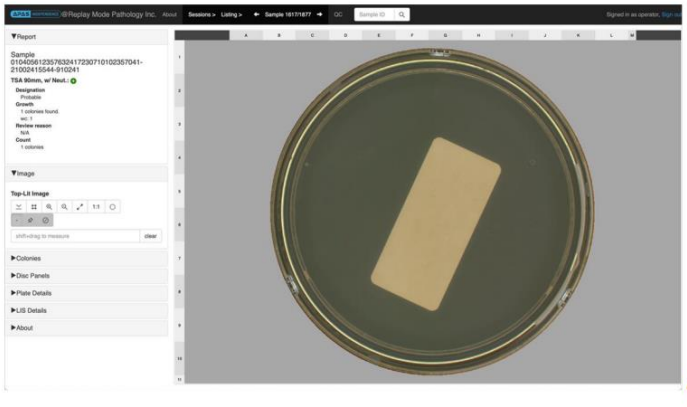
AZ Experience

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





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1. PharmaLab 2023, Automated Reading of Agar Plates using AI, Andrew Gravett, AstraZeneca

Secondary Validation – Example, AstraZeneca

- Propose a two-stage validation process.
- Establish expected performance –
  - A study to be run in-house using some contrived growth plates, number chosen to deliver the required confidence intervals and the number of no growth plates chosen to provide a reasonably high rate of positivity to ensure the human readers are reading in a representative manner. The negative number is otherwise unimportant.
- Establish in use performance of APAS –
  - The instrument treated effectively as a human plate reader. The plates will be sorted by APAS and then checked by a human plate reader, as per current process. The rate of corrections to be tracked. AstraZeneca could choose to have only a single manual read as the check of APAS, or retain the current two stage read.

AZ[1] - Key Points for Regulatory Opinion

- Once the model is “locked” and no longer learning, expect to follow normal laboratory change control GMP processes.
- What is the requirement for image storage?
  - In the manual process plates are discarded, and the raw data is the count.
  - There are sustainability and software speed challenges with storing 30,000 images a month.
  - Proposal to store images until batch release.
- Once validated, and because there is a secure audit trail and traceable data transfer from APAS to lab management system, what is requirement for a second check and/or any verification of a percentage of negative results or counts?
- What is the specific minimum expectation to define equivalent or better since there is some subjectivity in counting by humans?

[1] internal communication AZ / LBT October 2023 re interaction with EMA Quality Innovations Group.

Thank you

Appendix - Resources for industry

- ISPE Gamp 5 v2 A Risk-Based Approach to Compliant GxP Computerised Systems. Appendix D11 – Artificial Intelligence and Machine Learning (AI/ML). July 2022
- ISPE March / April 2022 AI Maturity Model for GxP Application: A Foundation for AI Validation.
- FDA CDER Artificial Intelligence in Drug Manufacturing – discussed in FDA/PQRI (Product Quality Research Institute) Workshop on the Regulatory Framework for the Utilization of Artificial Intelligence in Pharmaceutical Manufacturing. Sept 26-27, 2023