CASSS WCBP 2017: PLENARY COLLABORATING TO ACCELERATE BIOPHARM’S MANUFACTURING INNOVATION: A TECHNOLOGY ROADMAP UPDATE

Reed Harris, Beth Junker, Patrick Swann, Jeff Weber, Jonathan Dakin

26th January 2017
Overall Agenda

- Introductions
- BioPhorum Operations Group (BPOG) Introduction: Jonathan
- BPOG Technology Roadmap Overview: Beth
- In Line Monitoring / Real Time Release: Patrick
- Rapid Microbiological Methods: Jeff
- Q&A
Introductions

- Jonathan Dakin, BPOG
  - Regulatory Interaction Lead and Facilitator
- Beth Junker, Consultant
  - BioProcess Advantage LLC
- Reed Harris, Genentech, a member of the Roche Group
  - Senior Staff Scientist, Pharma Technical Development (Biologics)
- Patrick Swann, Biogen
  - Vice President, Regulatory Affairs
- Jeff Weber, Pfizer
  - Senior PAT Project Manager
Introducing BPOG

Jonathan Dakin
What is BPOG?

- Unique global collaboration
- Powerful vehicle for change
- 6 Phorums
- >50 industry changing initiatives
- Industry leaders and experts working in concert
- Delivering results by pooling knowledge, practices and ideas
BPOG is a collaboration of the World’s top biopharma manufacturers and supply partners

<table>
<thead>
<tr>
<th>Abbvie</th>
<th>Alexion</th>
<th>Amgen</th>
<th>AstraZeneca</th>
<th>Bayer</th>
<th>Biogen</th>
<th>Cook Pharmica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynavax Technologies</td>
<td>Eisai</td>
<td>Ferring Pharmaceuticals</td>
<td>Fujifilm Diosynth Biotechnologies</td>
<td>G-Con Manufacturing</td>
<td>GE Healthcare</td>
<td>Genentech</td>
</tr>
<tr>
<td>Genzyme A Sanofi Company</td>
<td>GSK GlaxoSmithKline</td>
<td>ImmunoGen, Inc.</td>
<td>Janssen</td>
<td>Kaiser Optical Systems, Inc.</td>
<td>Lilly</td>
<td></td>
</tr>
<tr>
<td>Lonza</td>
<td>MSD</td>
<td>Merck</td>
<td>Novartis</td>
<td>Novavax</td>
<td>Novo Nordisk</td>
<td>Pall</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Regeneron</td>
<td>Roche</td>
<td>Samsung</td>
<td>Sanofi</td>
<td>Sartorius Stedim Biotech</td>
<td>Shire</td>
</tr>
<tr>
<td>Takeda</td>
<td>ThermoFisher Scientific</td>
<td>UCB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BPOG Mission

To create an environment where the global biopharmaceutical industry can collaborate and accelerate their rate of progress, for the benefit of all

We do this by

- **Bringing leaders together** to create future visions that focus the industry’s energy on the key emerging opportunities
- **Mobilising communities of the top experts** around these opportunities, up and down the biopharma value chain
- **Creating partnerships that enable change** and provide the quickest route to implementation and results
- **Replacing isolation with collaboration** so that the industry shares, learns and builds the best solutions together

**Making the journey Better, Faster, Cheaper**
BPOG works so well as it is

- **Focused** on biologics process development and manufacturing

- **Influential** as almost every global company is a member

- **Strategic** as sponsorship comes from the most senior leaders

- **Representative** as conclusions are drawn from industry wide experience

- **Results driven** with a clear mission to improve and create benefit for all

- **Professionally facilitated** in every team
Benefits of membership come at many levels

1. Contacts and networks
2. Comparison of competence
3. Shared experience and knowledge
4. Co-developed best practices and adoption approaches
5. Industry engagement with regulators
6. Synchronised implementation of change
BPOG: 6 Phorums covering all aspects of biopharma operations

Drug Substance, Fill Finish, Development, Information Technology
Accelerating the way the industry delivers near term results, making best practice development and implementation faster, cheaper and smarter

Supply Partner Phorum
Creating the supply chains the industry needs; defining, developing and implementing solutions for business processes, systems and culture

Technology Roadmapping
Revolutionising the way the industry develops longer term transformational manufacturing and technology capabilities
Focusing on strategy and 10yr time horizon, defining needs, difficult challenges and potential solutions

Regulatory Interaction
Ensure efforts to design and adopt advances in manufacturing are aligned through engagement with Health Agencies

BPOG Facilitation
Decisions are made at the right time, at the right place by the right people
Linkages are made visible to avoid redundancy
Synergies are leveraged through effective coordination
## Fill Finish

### Mission

To solve near term challenges together and develop the safe, predictable, lean and agile processes needed in our drug product operations

### Benefits

- **Reduce EM lead-times and costs through fast adoption of rapid micro by exploiting harmonised industry qualification protocols**

- Reduce risk and isolator operating costs by scaling back settle plate use – worth $100m across the industry

- Follow best bio EM deployment practices and ensure the best control for investment in a new faculty

- Reduce lyo engineering runs, $m in costs and lost production during process develop and tech transfer by running a qualified model at commercial scale

- Reduce particle contamination on traditional stoppers by working as a consortium with the suppliers

- Use an industry risk based method to classify visible particles to increase confidence and simplify dispositioning and release decisions

### Membership

- BioPharma manufacturers with own or contracted out sterile filling operations and CMOs.

- Suppliers invited in as guests to address commodity related problems

---

18 Member companies

7 Workstreams

300 people
COLLABORATING TO ACCELERATE BIOPHARM’S MANUFACTURING INNOVATION: A TECHNOLOGY ROADMAP UPDATE

Beth Junker
A strong collaboration, bringing the industry’s top people together to contribute to & benefit from the technology roadmap

- Developed a strong Steering Committee
  - Required decision making
  - Driving roadmap
  - Subject matter experts access

- Diverse participants
  - 17 biomanufacturers
  - 12 supply partners recently joined (and growing)
  - Academics & regional hubs, e.g. MIT, AMBIC, CPI, SEDB, NIIMBL

- Over 160 people involved globally

<table>
<thead>
<tr>
<th>Biomanufacturers</th>
<th>Supply Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbvie</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Thermo Fisher</td>
</tr>
<tr>
<td>Bayer</td>
<td>MilliporeSigma</td>
</tr>
<tr>
<td>Biogen</td>
<td>Sartorius Stedim</td>
</tr>
<tr>
<td>Fujifilmdb</td>
<td>Kaiser Optical</td>
</tr>
<tr>
<td>GSK</td>
<td>PM Group</td>
</tr>
<tr>
<td>Immunogen</td>
<td>G-Con</td>
</tr>
<tr>
<td>Janssen</td>
<td>Novasep</td>
</tr>
<tr>
<td>Lonza</td>
<td>M+W</td>
</tr>
<tr>
<td>Merck MSD</td>
<td>CRB</td>
</tr>
<tr>
<td>EMD Serono</td>
<td>Pall</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Asahi Kasei</td>
</tr>
<tr>
<td>Roche</td>
<td></td>
</tr>
<tr>
<td>Sanofi</td>
<td></td>
</tr>
<tr>
<td>Shire</td>
<td></td>
</tr>
<tr>
<td>Takeda</td>
<td></td>
</tr>
<tr>
<td>UCB</td>
<td></td>
</tr>
</tbody>
</table>
High Level Roadmap structure

Industry Trends
Business Drivers

Payer pressure on cost
Diversification of product groups
In region manufacturing
Personalised medicine

Speed  Cost  Flexibility  Quality

Drug Product – Low volume high value
Drug Product – High volume low value
Drug Substance – Large scale stainless steel
Drug Substance – 2K scale SUS Continuous USP
Drug Substance – 2K scale SUS Batch USP
Drug Substance – <500L scale Continuous

BPOG Introduction
Expert teams mobilised to develop roadmaps for six key enabling technology areas

<table>
<thead>
<tr>
<th>Roadmap Team</th>
<th>Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process Technology</strong></td>
<td>Process Intensification: Highly concentrated systems - combining multiple unit operations</td>
</tr>
<tr>
<td></td>
<td>Continuous Processing: New separation and media technologies, coupled with advanced automation and process control</td>
</tr>
<tr>
<td><strong>Modular and Mobile</strong></td>
<td>Quick to configure and assemble manufacturing systems using ‘plug and play’ standard designs</td>
</tr>
<tr>
<td><strong>In-line Monitoring &amp; Real-time release</strong></td>
<td>Process control and product quality through advanced monitoring devices, indirect or multi-attribute sensors and PAT</td>
</tr>
<tr>
<td></td>
<td>Global regulatory testing standards, advanced process control strategies and raw material characterization</td>
</tr>
<tr>
<td><strong>Fully Automated Facility</strong></td>
<td>Scale up with a focus on automation, equipment and biology results in a fully automated facility</td>
</tr>
<tr>
<td><strong>Supplier Management</strong></td>
<td>Suppliers become technology development partners for our industry, collaborating to solve problems</td>
</tr>
<tr>
<td><strong>Knowledge Management</strong></td>
<td>Integrated knowledge of product and process technology across development, manufacturing and commercial value streams</td>
</tr>
</tbody>
</table>
Process Technologies – Key Themes

Streamlining unit operations
- Incremental efficiencies
- Culture shifts
- Future targets for performance

Linking upstream & downstream
- Continuous processing
- High value ‘hotspots’

Disruptive Technologies
- Matched to operational needs
- Integral to performance acceleration

Faster process improvement
- Regulatory impact
- Cohesive validation
Modular & Mobile – Key Themes

**Standardization**
- Creation of equipment standards
- Enable multi-supplier environment
- Regulatory harmonisation

**‘Facility as Equipment’**
- Management of validation, capital & speed to install
- Eliminate non-value add activity (manufacturers & regulators)

**Flexibility**
- Quick, easy scale up of processes & facilities
- Bring production to where most needed – closer to patients
- Speed to market

Paradigm shift in approach to management of factory infrastructure
In-line Monitoring & Real-time Release (ILM / RTR) – Key Themes

- Unlock potential for robust process control while improving quality & operational efficiency
- End-to-end methodology, through lens of biomanufacturing scenarios
- Over past decades, key bottleneck has been batch disposition
  - Today, starts at end of production with analytical tests & requires long-lead time; mainly human operated, paper-driven system
  - Opportunity to reduce to within hours to a few days
- Enabled by integration & advancement of several elements:
  - Raw material characterization & control
  - Hardware: advanced in line monitoring, in-direct or multi-attribute sensors
  - Software for closed feedback control, multivariate analysis for predictive models
  - Rapid analytical testing for biological assays
  - Streamlined quality & business systems: review by exception
- Several technologies, methodologies & regulatory guidance required
  - Future technology critical to successfully achieving real-time release
Timing of publication, communications & feedback mechanism

- **1st edition published in May 2017, freely available on BPOG website**

- Complemented by broad communications mix
  - Webinars, conference presentations, articles, newsletters

- Request input on roadmap’s content & scope of future editions
  - Individual comments or formal response from your organisation
  - Your organisation becoming active members of the collaboration

- Roadmapping is about stimulating an industry response, encouraging required innovation to happen

- What solutions can you bring to overcome difficult challenges facing the industry?
Summary

- **Strong Technology Roadmap collaboration well established**
  - Biomanufacturers, suppliers, regulators, academics, regional hubs

- **Solid business benefits identified**
  - Unified industry needs to align efforts across stakeholders
  - Substantially change risk-reward profile of new technology development

- **Integrated teams built close partnerships**
  - Pooled effort on pre-competitive potential solutions
  - Enable fast adoption (e.g., identify rapid prototyping opportunities)

- **2017 provides an opportunity to accelerate change together!**
  - Receive & incorporate feedback for further improvement in Roadmap 2nd Edition
    - Deeper dives into critical areas & extend to adjacent areas not previously covered
  - Work closely to achieve rapid development & demonstration of new technologies
    - Influence required fundamental R&D efforts
  - Use combined knowledge & experience to address identified regulatory challenges
Questions and Discussion

- Opportunity to discuss approaches to technical/regulatory challenges for successful implementation of new technologies:
  - In-Line Monitoring & Real-time Release
  - Rapid Microbiology Methodologies

- Soliciting your ideas on how to:
  - Increase value proposition for In-Line Monitoring & Real-Time Release
  - Ensure Supply Partners, Regulators, Academics & Regional Hubs remain closely involved & aligned with the implementation & further development of Technology Roadmap strategies
In-Line Monitoring & Real Time Release

Patrick Swann and Reed Harris
Questions

• What can we do to increase the value proposition for In-line Monitoring / Real Time Release (ILM/RTR)?
• Are there other technologies not considered that could enable ILM/RTR?
• What else do you want to see in the roadmap?
• What do you see as the major technical / regulatory challenges / milestones (impediments) to successful implementation of ILM/RTR?
• Are there other ideas to accelerate timelines?
Summary

- Today, batch disposition starts at the end of the production batch, and requires long-lead time analytical tests with human oversight and review.
- This report explores inline monitoring / real-time release as process controls to improve product quality and operational efficiency.
- Technology roadmap tables are provided illustrating gaps in current industry and ideas of how to close those gaps over the next several years.
# Value Proposition

<table>
<thead>
<tr>
<th>Roadmap Team</th>
<th>Vision</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-line Monitoring and Real-time release</td>
<td>Process control and assurance of product quality through advanced monitoring devices, multi-attribute sensors, and PAT.</td>
<td>• Tighter product and process control</td>
</tr>
<tr>
<td></td>
<td>Complete batch disposition package contemporaneous with completion of manufacture</td>
<td>• Early issue identification</td>
</tr>
<tr>
<td></td>
<td>Global regulatory testing standards consistent with these control strategies.</td>
<td>• Reduction in waste and errors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Eliminate $Bn’s of inventory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Product released 1-2 days after manufacture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Reduced time needed for QA review</td>
</tr>
</tbody>
</table>
## Upstream Quality Attributes or Process Parameters

<table>
<thead>
<tr>
<th>Attribute or Parameter</th>
<th>Current State</th>
<th>Technology in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>In-line pH probes</td>
<td>Robust single use sensors with feedback control</td>
</tr>
<tr>
<td>Dissolved O2, CO2</td>
<td>On-line blood gas Analyzers, off-gas analysis by MS and IR In-Line DO Probes</td>
<td>In-Line CO2 probes</td>
</tr>
<tr>
<td>Glucose</td>
<td>At-line and On-line glucose analysis</td>
<td>In-line Raman, NIR with feedback control; Enzymatic chip based sensors</td>
</tr>
<tr>
<td>Amino Acids</td>
<td>Off-line</td>
<td>On-Line UPLC</td>
</tr>
<tr>
<td>Glycan distribution</td>
<td>Off-line</td>
<td>On-line UPLC-MS</td>
</tr>
<tr>
<td>Charged isoforms</td>
<td>Off-line</td>
<td>On-line UPLC, IEC</td>
</tr>
<tr>
<td>Glycation</td>
<td>Off-line</td>
<td>On-line Intact Mass</td>
</tr>
</tbody>
</table>

In-line: sample is not removed from the process stream; can be invasive or noninvasive ("sensors").

On-line: sample is diverted and may be returned to the process stream.
# Downstream Quality Attributes or Process Parameters

<table>
<thead>
<tr>
<th>Attribute or Parameter</th>
<th>Current State</th>
<th>Technology in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregates</td>
<td>Off-line SEC</td>
<td>On-line UPSEC, In-line MALS, MIR</td>
</tr>
<tr>
<td>Charge heterogeneity</td>
<td>Off-line CE or IEX</td>
<td>On-line UPLC</td>
</tr>
<tr>
<td>[protein]</td>
<td>In-line UV, In-line refractive index</td>
<td>Multi-wavelength diode arrays for column elution</td>
</tr>
<tr>
<td>HCP</td>
<td>On or at-line ELISA</td>
<td>At-line Mass Spectrometry</td>
</tr>
<tr>
<td>Potency (off-line testing)</td>
<td>3–5 day cell-growth assays</td>
<td>1–2 day reporter gene assays</td>
</tr>
</tbody>
</table>

On-line: sample is diverted and may be returned to the process stream
At-line: sample is removed, isolated from and analyzed in close proximity ("tested on the factory floor")
## Opportunities for New Technologies

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Current Technologies</th>
<th>Current Turnaround time</th>
<th>Potential Technologies</th>
<th>Target Turnaround time</th>
<th>Target Sensitivity or Range</th>
<th>Target Product Pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro, Viral Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioburden</td>
<td>Pour plate method</td>
<td>7 days</td>
<td>Fluorescence based plate assays. Respirometry, Microflow imaging, flow cytometry</td>
<td>2 days</td>
<td>1 CFU / 10 mL</td>
<td>Multiple</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>Cultivation assay</td>
<td>28 days</td>
<td></td>
<td>2 days</td>
<td>Negative</td>
<td>Cell culture fluid</td>
</tr>
<tr>
<td>In Vitro (adventitious) Virus</td>
<td>Cultivation assay</td>
<td>28 days</td>
<td></td>
<td>2 days</td>
<td>Negative</td>
<td>Cell culture fluid</td>
</tr>
<tr>
<td>MMV</td>
<td>qPCR</td>
<td>2 days</td>
<td>qPCR (no change)</td>
<td>2 days</td>
<td>Negative</td>
<td>Cell culture fluid</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>LAL</td>
<td>1 day</td>
<td>Cartridge-based endotoxin testing, Mass Spectrometry</td>
<td>1 day</td>
<td>0.01 EU/mL</td>
<td>Multiple</td>
</tr>
</tbody>
</table>
Future Needs – High Level

1. In-line monitoring and integration of in-line probes with process control systems
2. Innovative in-line multi-attribute sensors
3. Predictive analytics
4. International regulatory acceptance of alternative approaches
Future Needs – Mid Level

In-line monitoring and sensors
- Rapid inline product quality measurements
- Sensitive and robust measurement
- Standardized interface
- Sensors reusable / disposable

Predictive Analytics
- Modelling
- Scale-down / miniaturization
## International Regulatory Acceptance

<table>
<thead>
<tr>
<th>Issue/Challenge</th>
<th>Opportunity</th>
<th>Engagement Plans</th>
<th>Proposals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global acceptance of RTR</td>
<td>Provide more support for wider industry use and global regulatory acceptance</td>
<td>Work on risk assessment for release and process control.</td>
<td>Knowledge sharing with FDA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk assessment consistent with ICH Q9 and compares/contrast with risk assessment</td>
<td>Presentations &amp; Publications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for current state control strategies</td>
<td></td>
</tr>
<tr>
<td>Development of Rapid Micro Methods and Testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diverse Global Regulatory Requirements</td>
<td>Harmonization (ICH and WHO)</td>
<td>Systematically identify country/regional specific impediments to ILM/RTR</td>
<td>Presentations at international meetings</td>
</tr>
</tbody>
</table>

Advantage: reduction of errors and waste
Future Needs – More Detailed

In-line Monitoring & Sensors
- Multi-attribute (ideally in single port)
- Must fit standard port specifications
- Single or no calibration; at least easy
- CIP/SIP/caustic stable/pressure stable
- Sensors with capability to monitor their own performance and predict when they will fail
- Small instrument footprint
- Centralized or remote access
- Software interface with distributed control system
- Scalability (scale down)
- Moderate sample frequency (min – hours)
- Material Qualification Documents

User requirements list under development by SME’s from Supplier and Biopharmaceutical Companies
## Specific Metrics of Success for ILM/RTR example: viral safety

<table>
<thead>
<tr>
<th>METRIC</th>
<th>Description</th>
<th>Current</th>
<th>2019</th>
<th>2022</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>METRIC</td>
<td>Reduction in turnaround times for adventitious virus testing from 28 days to 2 days</td>
<td>0% implementation</td>
<td>0%</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td>NEED</td>
<td>Develop/validate methods to generate rapid results.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHALLENGE</td>
<td>Obtaining world-wide acceptance from health authorities for use of new technologies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>POTENTIAL SOLUTION</td>
<td>Possible next-generation sequencing, qPCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# ILM/RTR Metrics of Success for Tech Roadmap

<table>
<thead>
<tr>
<th>Metric</th>
<th>5 yr Target</th>
<th>Impact</th>
<th>10 yr Target</th>
<th>Impact</th>
<th>Impact notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of non-quality</td>
<td>10% of operating cost</td>
<td>Medium</td>
<td>2% of operating cost</td>
<td>High</td>
<td>Greater control + detectability due to in-line monitoring and RTR</td>
</tr>
<tr>
<td>Time to Product availability</td>
<td>50% reduction (2 months)</td>
<td>Medium</td>
<td>90% reduction (2 weeks)</td>
<td>High</td>
<td>Ability to release in real time will allow team to react quicker to potential stockouts</td>
</tr>
</tbody>
</table>
Discussion

▪ What can we do to increase the value proposition for in-line monitoring and real-time release?
▪ Are there other technologies not considered that could enable ILM/RTR?
▪ What else do you want to see in the roadmap?
▪ What do you see as the major technical / regulatory challenges/milestones (impediments) to successful implementation of ILM/RTR?
▪ Other ideas to accelerate timelines?
Rapid Micro Methods:
Continuous Microbiological Monitoring for Reduced Interventions & Elimination of Settle Plates

Jeff Weber
BPOG Fill Finish Workstream
Summary

Objective: Continuous Micro Monitoring to Reduce Interventions

Deliverable: White paper on the case for eliminating/reducing settle plates using Bio-Fluorescent Particle Counting (BFPC) as an alternative, with the goal of gaining Agency feedback to inform the workstream's strategy and support Agency acceptance.
Continuous Micro Monitoring

Demonstrate system capability with open data sets.

*10 days of Grade A White Paper*

Quality oversight response.

*Sample Capture device. Statistical review of Alert / Action Limits*

Data integrity for interventions

---

Reduced Interventions

Impact of Placing / Recovery of Plates

*Confirm theory that placing plates in critical zones is high risk*

Training and fewer personnel interacting with processes

---

Elimination of Settle Plates

Demonstrate state-of-control during manufacturing

Activity impact with temporal resolution

*Improved data integrity and process knowledge*
What is Bio-Fluorescent Particle Counting?

Active air particle counter that simultaneously monitors **biological fluorescence** (ATP, NADH, picolinic acid), **particle count** and **size** information.
Current Status

▪ Implementation gaps have been identified
  • Quality oversight / response to signals
    o EU GMP Annex I update
  • Identification of microorganisms
  • Gathering data sets without manufacturing risks
    o “safe harbor” during testing phase

▪ Draft of position paper – completed and reviewed
  • Needs data sets to demonstrate capability
    o Grade A area / 10 days of continuous data

▪ Additional Considerations:
  • Development of Sample Capture filter holder
Current Micro Lab Testing Volumes

- Water: 9%
- API/Raw Mtls: 1%
- Finished: 3%
- Environmental Monitoring: 85%
- Other: 2%

- Automation of RODAC, Grade B,C,D Settle Plates
- Elimination of Grade A Settle Plates
- 50% of EM at Aseptic Sites
- 50% of EM at Aseptic Sites
CFU ≠ AFU

- **Colony-forming unit (CFU)** is a unit used to estimate the number of viable bacteria or fungal cells in a sample.

- **Auto-Fluorescent Unit (AFU)** is a unit that reflects both size and fluorescence of the particle.
10 Days Non-Viable

Active Air Particle Counting - Grade A - At Rest

Action Limits: 3520 for 0.5 micron and 20 for 5 micron
10 Days - AFU

BioFluorescent Particle Counting - Grade A - At Rest

21:44 hours

5 AFU / 402 m³ = 0.01 AFU/m³

Action Limit: <1 CFU/m³
False Positive Signals

- Polymers, dead cells, pollen, some solvents...
- "Viable But Not Culturable" (VBN C) microorganisms.

- Requires sample capture to identify false positives and samples.

- Limitation of Growth Media ~ 0.1%
False Negative Signals

- ATP is found in all microorganisms – *universal detection*
- Potential desiccation of captured samples
Implementation Pathway

- **Data Sets from several sites**
  - 24, 48, and 96 hour of stable operation
  - Quality input for interventions and Action/Alert levels

- **Socialize the concept across industry:**
  - Articles, podium presentations and BPOG workgroup.
  - Training package
  - White papers: *continuous micro monitoring, investigations, room recovery rates, B/C/D areas*

- **Agency training**
  - Agency leadership
    - Technical and compliance groups.
  - Field Auditors

In-process

2Q2017

2Q2017 Publication

Pending data set completion
Discussion

1. How to develop an Industry approach to Implementation and Reg Acceptance of new technologies e.g. Rapid Micro Methodologies

2. What forum can be used to engage Agencies for timely feedback for newer online PAT / RMM platforms?
   The current “submit and reply” format takes several years and companies often face the never ending challenge to prove equivalency versus reviewer opinions

3. Each Agency has different expectations for acceptance of methods, this can be several dozen meetings or filings, how can we move towards reciprocity between Agencies?

Amy.McDaniel@pfizer.com or Jeffrey.W.Weber@pfizer.com
Thank You
Questions

**Technology Roadmap**
- How to realise these opportunities through keeping regulations and decisions relevant and up to date?
- How to ensure Supply Partners, Regulators and Academics closely involved and aligned to Industry Technology Direction?
- How to introduce new technologies in a Regulatory Environment and Globally?
- What are your expectations and what can be achieved by a Technology Roadmap?

**ILM/RTR**
- What can we do to increase the value proposition for in-monitoring and real-time release?
- Are there other technologies not considered that could enable ILM/RTR?
- What else do you want to see in the roadmap?
- What do you see as the major technical / regulatory challenges/milestones (impediments) to successful implementation of ILM/RTR?
- What ideas to accelerate timelines?

**Rapid Micro**
- How to develop an Industry approach to Implementation and Reg Acceptance of new technologies e.g. Rapid Micro Methodologies?
- What forum can be used to engage Agencies for timely feedback for newer online PAT / RMM platforms?
- How to improve current format to reduce time and prove equivalency?
- Agencies may have different expectations for acceptance of methods - how can we move towards reciprocity between Agencies?
Questions