

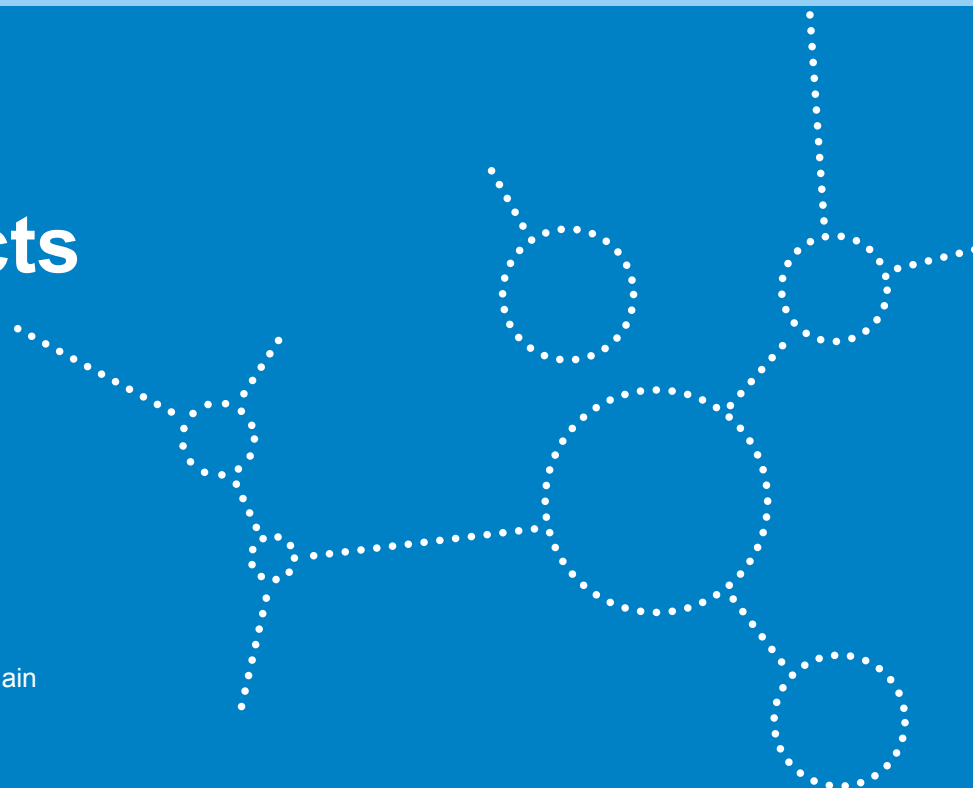
Process Analytical Sciences Group

# Application of PAT to support QbD in Bioprocessing

Jeffrey Doyle  
Manager – PAT Projects



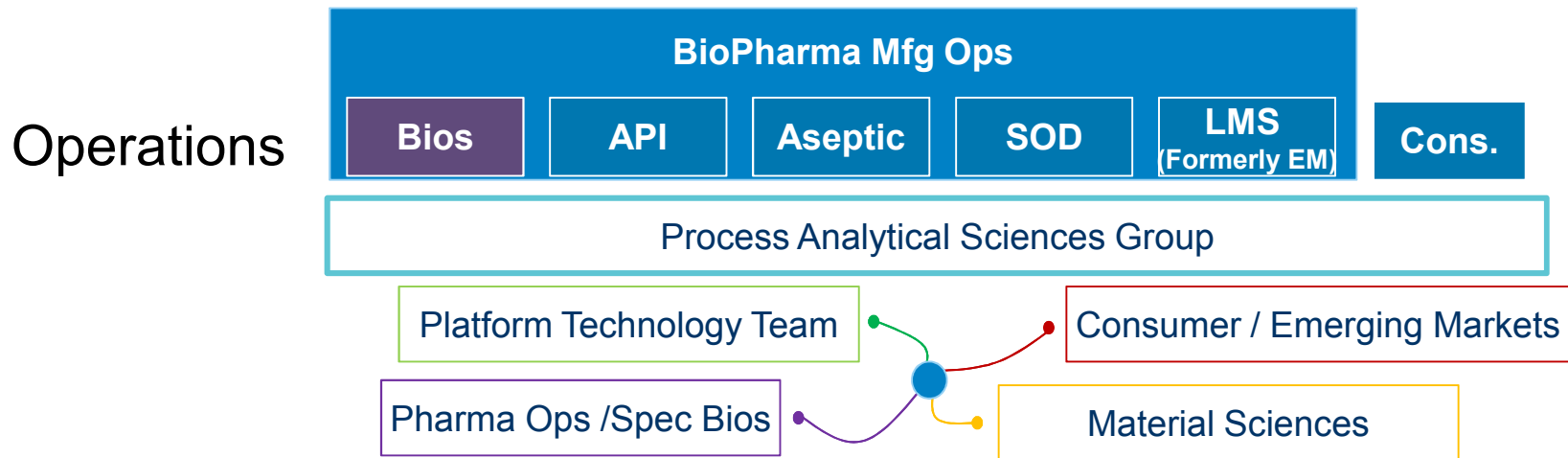
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# Worldwide Biopharmaceutical Company

77,000 employees supporting 3 business units

- Consumer/Vaccines/Oncology
- Global Innovative Pharma
- Global Established Pharma



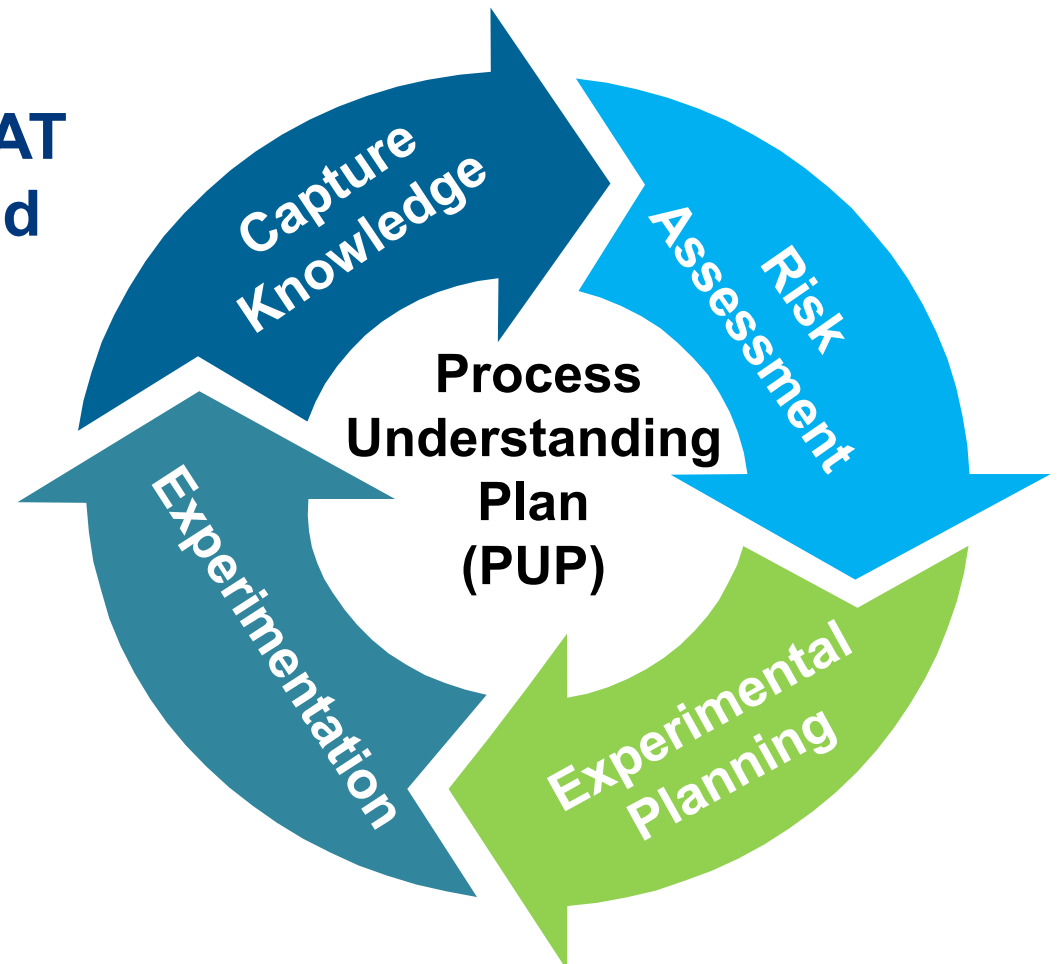
Algete | Andover | Grange Castle | Havant | Pearl River | Sanford | Strängnäs



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Application of PAT is considered during new process development as part of a systematic Right First Time (RFT) approach to QbD.

Pfizer's perspective on PAT and QbD is best described by our systems

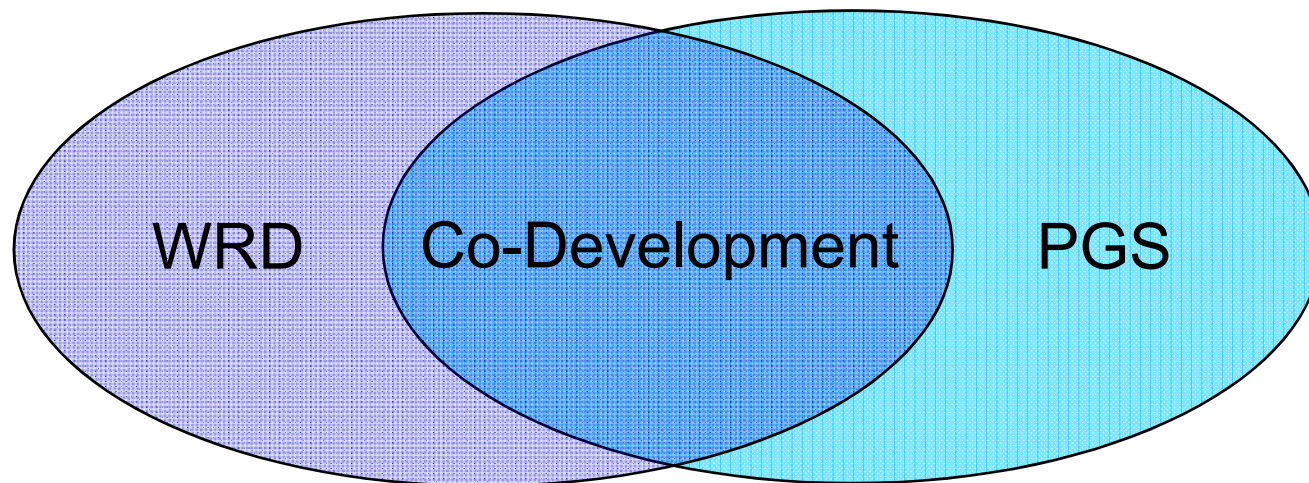


# New Process Development

## Utilizes a Co-Development approach:

Partnership between WRD and manufacturing (PGS) to jointly develop, scale-up and commercialize new products

Communication, engagement, planning and implementation at the “right” time



(Post-Proof of Concept Through Commercial Launch)



# What are the basic goals of a RFT approach to Co-Development?

## Establish functional relationships

- Identify significant parameters and attributes
- Identify & prioritize experimental strategy and required resources
- Document process understanding

## Translate process understanding into meaningful control ranges

- Strategically apply PAT



## What we do today is influenced by our past

- Participation in CBER's *Office of Biotechnology Products* (OBP) QbD Pilot
- High Level Strategy:
  - Risk assessments to identify Critical Quality Attributes
  - Risk assessments to identify Critical Process Parameters
  - Leverage scale down models to identify Design Space
- Outcome (BLA not filed):
  - Gained understanding of adaptive control and process optimization
  - PAT (measurement and control) application well received
  - Concern around change management within design space



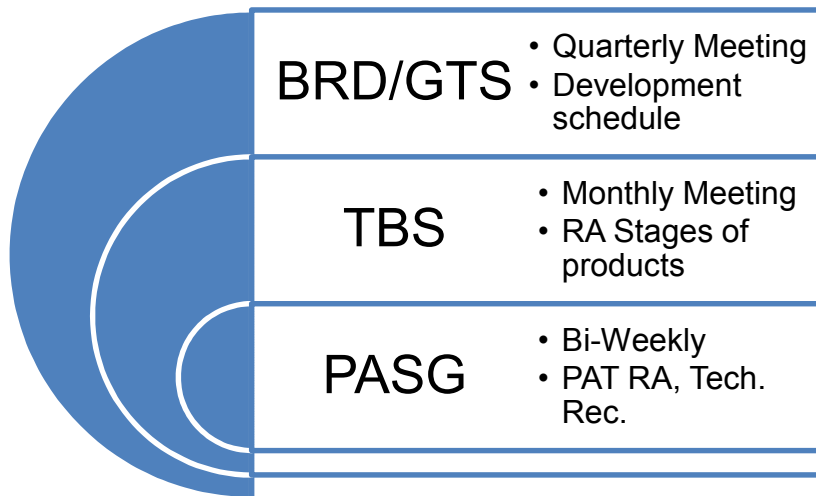
# Risk Assessment (RA) Approach to QbD

RFT RA	Timing	Typical Inputs	Typical Deliverables	Typical RFT Tools/ Templates
1 <sup>st</sup>	Prior to LPQ	<ul style="list-style-type: none"> <li>Initial CQA assessment</li> <li>Process Map</li> </ul>	<ul style="list-style-type: none"> <li>C&amp;E analysis (v1)</li> <li>Experimental Design (DoE)</li> <li><b>PAT strategy</b></li> <li>All above documented in Initial PUP</li> </ul>	<ul style="list-style-type: none"> <li>C&amp;E matrix</li> <li>Statistical design</li> <li>PUP template</li> </ul>
2 <sup>nd</sup>	Prior to Process Validation	<ul style="list-style-type: none"> <li>LPQ reports</li> <li>Experimentation PUP</li> </ul>	<ul style="list-style-type: none"> <li>C&amp;E analysis (v2)</li> <li>FME(C)A report (v1) with Risk Mitigation Plan</li> <li>Above captured in PUP +:                             <ul style="list-style-type: none"> <li>Initial PP Criticality</li> <li>Process Validation Criteria</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>FME(C)A</li> <li>C&amp;E matrix</li> <li>Statistical analysis</li> <li>PUP template</li> </ul>
3 <sup>rd</sup>	Prior to Regulatory Filing	<ul style="list-style-type: none"> <li>Validation Reports</li> <li>Updated CQA assessment</li> </ul>	<ul style="list-style-type: none"> <li>FME(C)A report (v2)</li> <li>Final C&amp;E update (if app)</li> <li>Updated PP Criticality</li> <li><b>Control Strategy</b></li> <li>Final PUP &amp; Design space</li> </ul>	<ul style="list-style-type: none"> <li>Statistical analysis</li> <li>FME(C)A</li> <li>C&amp;E matrix</li> <li>PUP template</li> </ul>

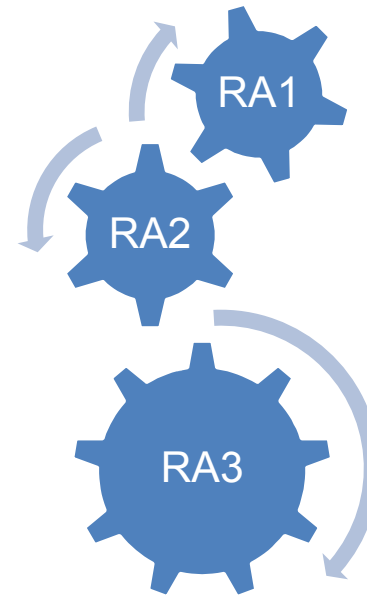
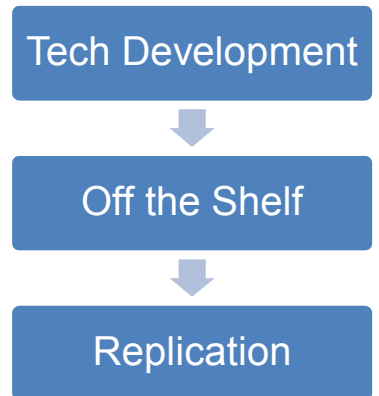


# The PAT Risk Assessment Strategy

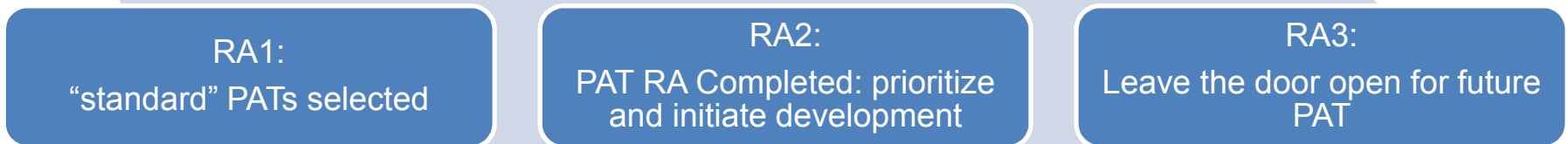
## How we stay involved



## Lead time we need

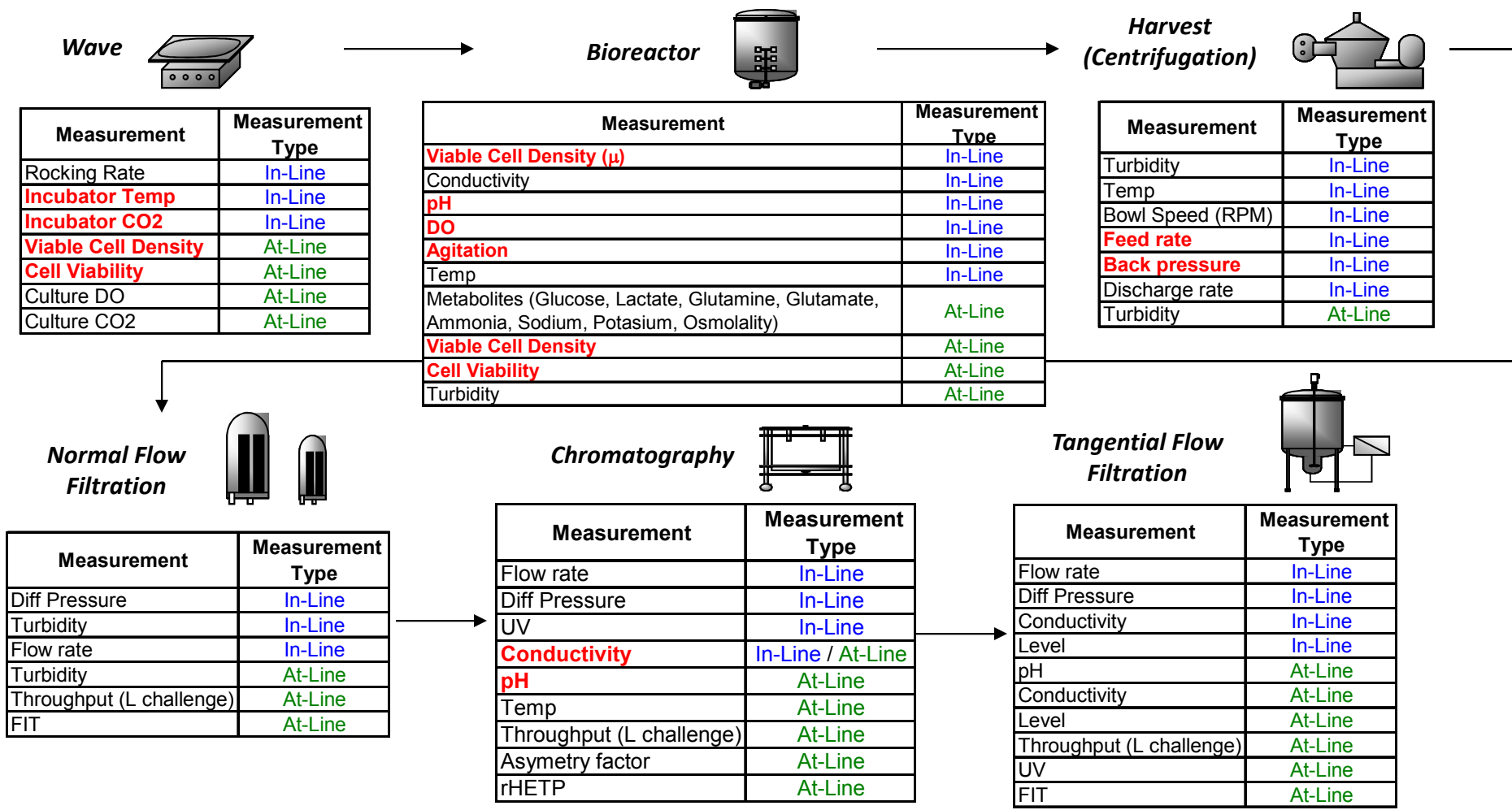


## The Lead time we have





# The Standard PAT List



**Measurement**

**PAT:** Critical process attributes relating to product quality, may be in-line or at-line measurements.

Potential PAT: Process analyzers that through data collection and analysis may relate to product quality.

**Measurement Type**

**In-line:** Measurement where the sample is not removed from the process stream.

**At-line:** Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.



# PAT Prioritization Assessment

## PAT for Process Control

List top ranking PAT for Process Control, only include quality attribute's that had a "criticality" score of medium or high.

- Several process control PAT strategies were identified as described below.

Focus Area	Key Quality Attribute	Current Measurement	PAT	Criticality	Probability of Success	Cost	Total Score	Comments	References	Selection
FA6: Production Bioreactor	glucose control profile range:	YSI	Process Trace (if glucose level less than 0.5g/L) - Strangnas	10	5	5	500	Risky vendor		
			[REDACTED]	10	5	10	1000	Additional POC work needs to be completed	PASG-RPT_1043 ,	Selected
			YSI 2700 Select Bio Analyzer – Andover	10	5	10	1000	Challenges with interfacing to bioreactor. Andover has YSI		
			BioProfile FLEX with aseptic autosampler	10	5	5	500	Pilot plant in Andover		
			Soft Sensor					Low robustness		
	Viable Cell Density / IVCC	Cedex	[REDACTED]	10	5	10	1000			
			Aber or equivalent Capacitance probe	10	10	10	2000	Already have this and selected for perfusion		Selected

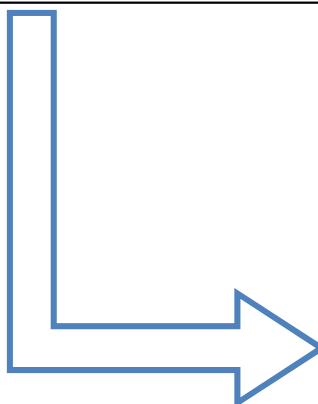
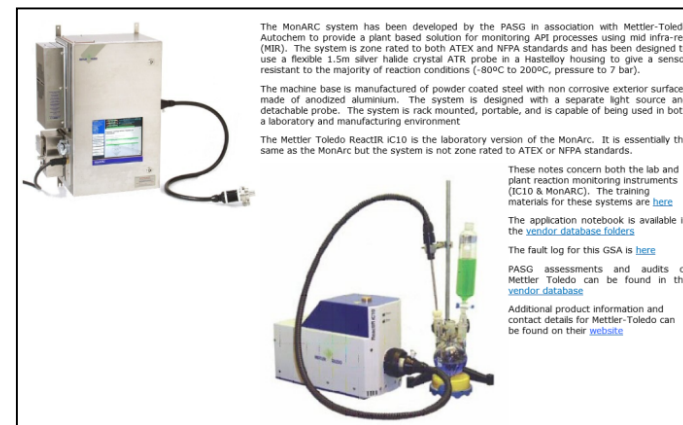


# Technology Choice Table

## Technology Choice Tables

The reference tables at the links below can be used to help decide which technology should be used for a specific application for a particular unit operation. Tables are included that list the recommended technology for unit operations for API, drug product, biologic API and aseptic manufacturing.

The tables also indicate if the technology is recommended for lab and/or plant use and if the application note book is available. Systems that are deemed available for lab and/or plant use and have a complete application notebook are termed Globally Supported Applications (GSAs). The table also highlights some applications currently under evaluation.



Application	Recommended System	Technology	GSA	Recommended Technology	Tech. under Evaluation
Raw material identity and <a href="#">conformity</a>	<a href="#">Bruker MPA</a>	NIR (bench)	✓		
	<a href="#">Foss Masterlab</a>	NIR (bench)		✓	
	<a href="#">Thermo Truscan</a>	Raman (handheld)	✓		
	<a href="#">Thermo PHAZIR</a>	NIR (handheld)	✓		
	<a href="#">Niton XRF elemental analysis</a>		X-ray fluorescence		
Fermentation (Reaction Monitoring)	<a href="#">ABB FTPA2000</a>	NIR	✓		
	<a href="#">Mettler Toledo Monarc</a>	Mid-IR	✓		
	<a href="#">Mettler Toledo IC10</a>	Mid-IR		✓	
	<a href="#">Kaiser Raman Rxn 1</a>	Raman		✓	
	<a href="#">Applied Analytics UV</a>		UV-Visible		



## Areas of PAT growth and next steps:

- **Continue to focus on the value proposition:**
  - Right First Time manufacturing (golden batch)
  - Process Understanding
  - Simply the ability to manufacture a robust product
  - Ensure reliable production to supply chain
- **Technology Development**
  - Use of Platform technologies
  - Venture Capital for small companies
  - Leverage Academia and grants
- **Utilization of PAT in conjunction with advanced control strategies**
  - Neural networks, advance process controllers



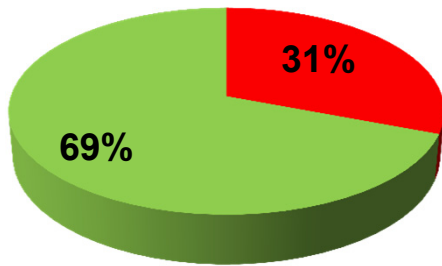
# Impact on Process Robustness

*Updated April 2014*

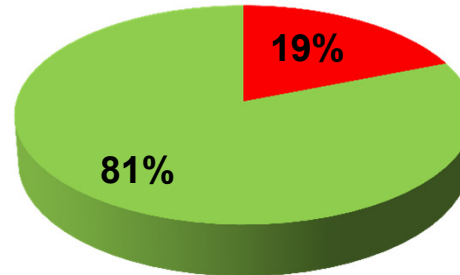
Green = Cpk>1

Red = Cpk<1

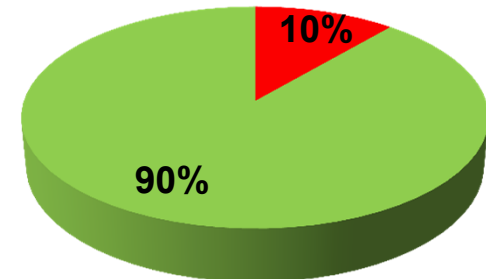
**In-Licensed**  
Updated 2012



**PGS – Legacy Products**  
1800 total attributes



**Co-Dev: QbD**  
201 total attributes



## Impact of PAT

**Average Cost Savings / Cost Avoidance – 2009 to 2012**

**\$4 Million / Year for 20 projects**



# Summary of Approach to PAT as part of QbD

- **Development**
  - Use quality risk management approach to select applications based on science that allow us to engineer in quality
- **Transfer to manufacturing**
  - Process understanding and inline measurements are valued within Pfizer
  - Control strategy is based on risk
  - PAT deployed based on prioritization
- **Quality Assurance**
  - Continued Process Verification – BPOG A-Mab
  - RTR for Bios is part of the active strategy



# Acknowledgements

- **Steve Hammond – Sr. Director, PASG**
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