

Process Analytical Technology:

**Innovation supporting Right First Time
in Pfizer Global Manufacturing**

IMB/Industry meeting Oct 23rd 2008

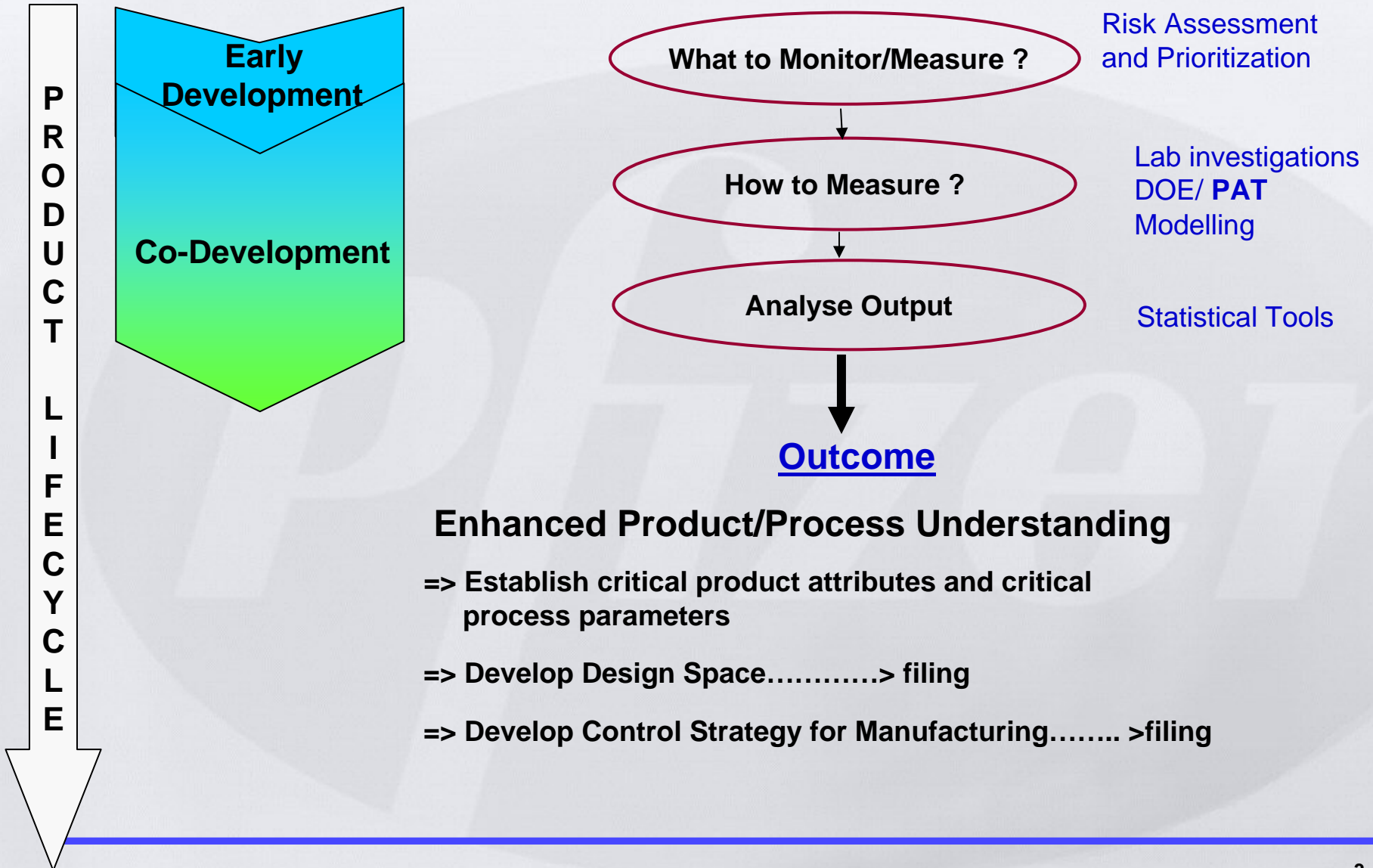
Conor McSweeney

Process Analytical Support Group

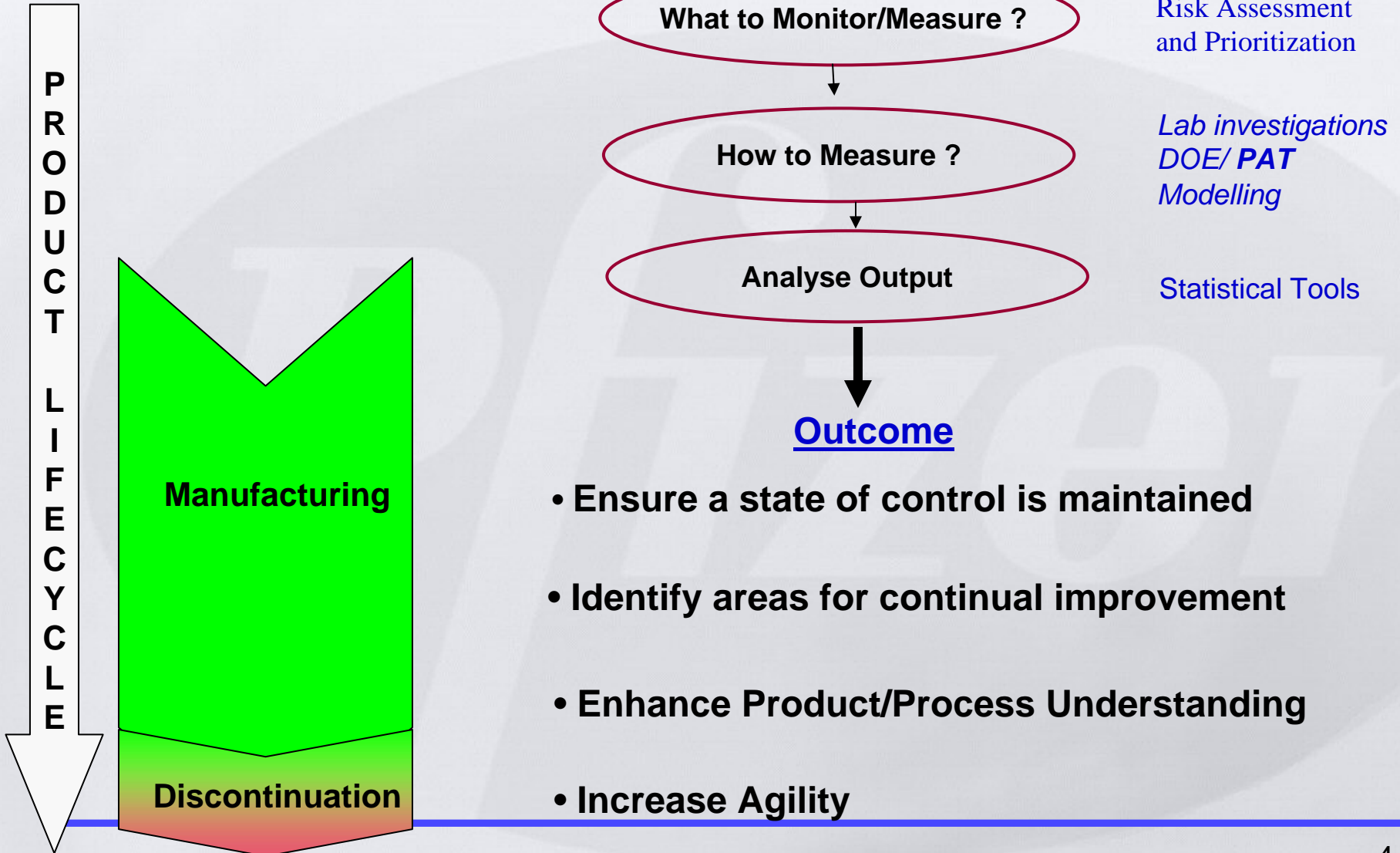
Integration of Q8,Q9,Q10 at Pfizer

- Pfizer now has a single global quality organisation. This facilitates a single Pfizer Quality system incorporating Development and Manufacturing
- Pfizer uses a product lifecycle management approach to maximise the benefits of quality by design, quality risk management and quality systems
- Pfizer is using a QbD approach for all new products
- Two QbD submissions approved to date
- CQV and RTR pilots underway

Monitoring in Development & Co-Development



Product/Process Monitoring in Manufacturing



PAT – Innovation enabling RFT manufacturing

- **PAT is a set of tools which can be applied to achieve a goal, not a goal in its own right**
- **The goal is to reduce variation in our processes – achieve Right First Time manufacturing**
- **PAT provides a window to enhance process understanding**
- **PAT is applied based on comprehensive process risk assessments as part of an overall strategy to enhance RFT manufacturing**
- **PAT can be used to enhance process safety**
- **PAT can enable a more cost effective and agile manufacturing operation**
- **PAT can help to monitor what matters**
 - **Development of knowledge space during development**
 - **Maintaining state of control during manufacturing**

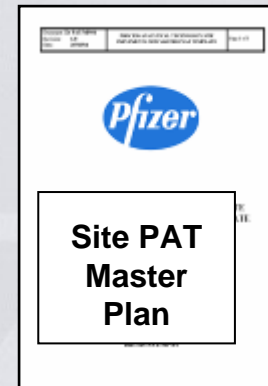
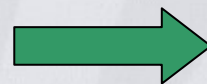
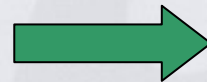
HOW PAT PROJECTS ARE IDENTIFIED AND PRIORITISED IN PGM

Existing manufacturing processes

- *PAT requirements identified and prioritised by cross functional process experts/ process teams based on experience, process capability, process understanding requirements, safety and quality drivers*

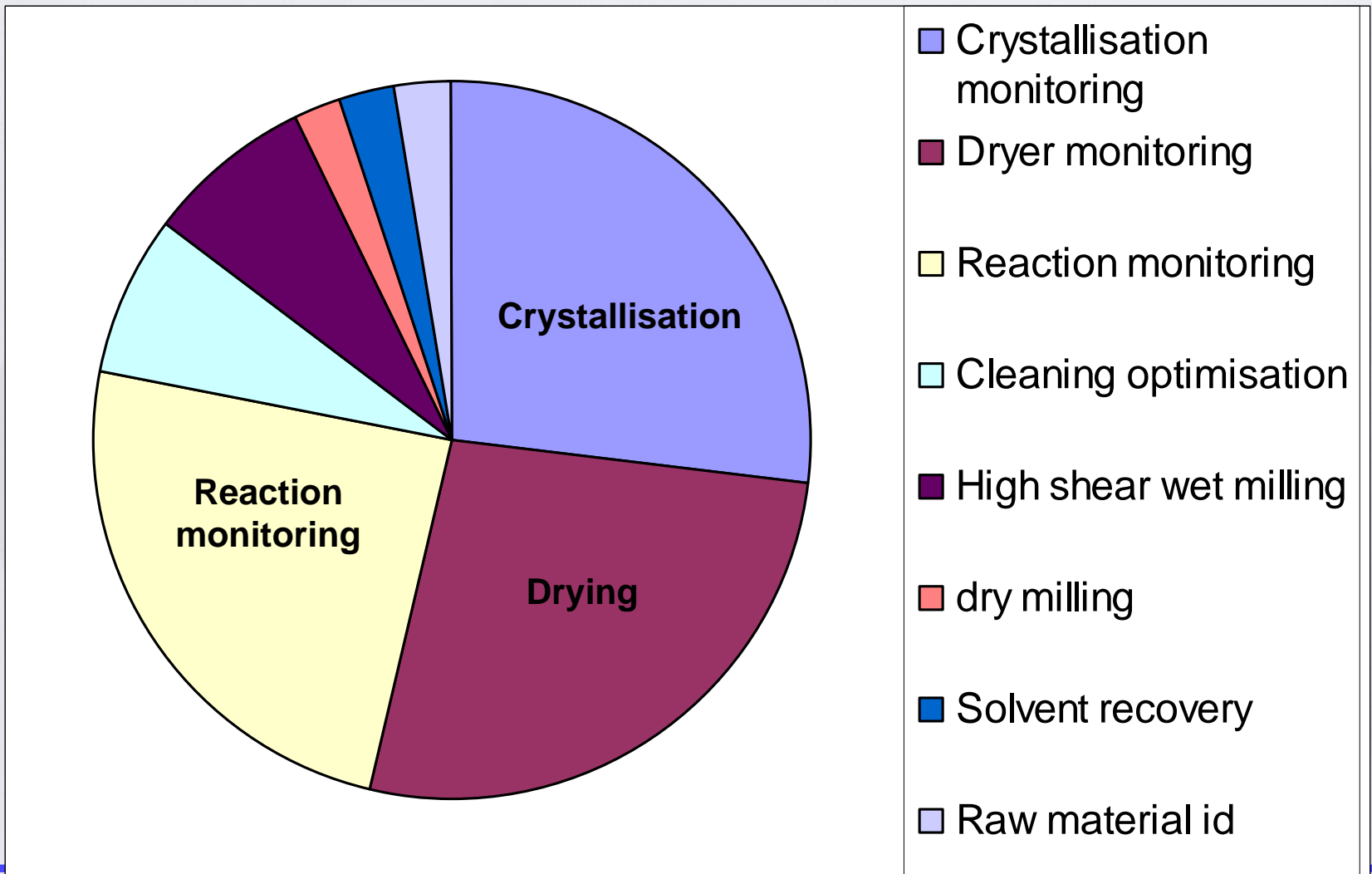
New manufacturing processes

Comprehensive RFT risk assessment to identify PAT measurement needs

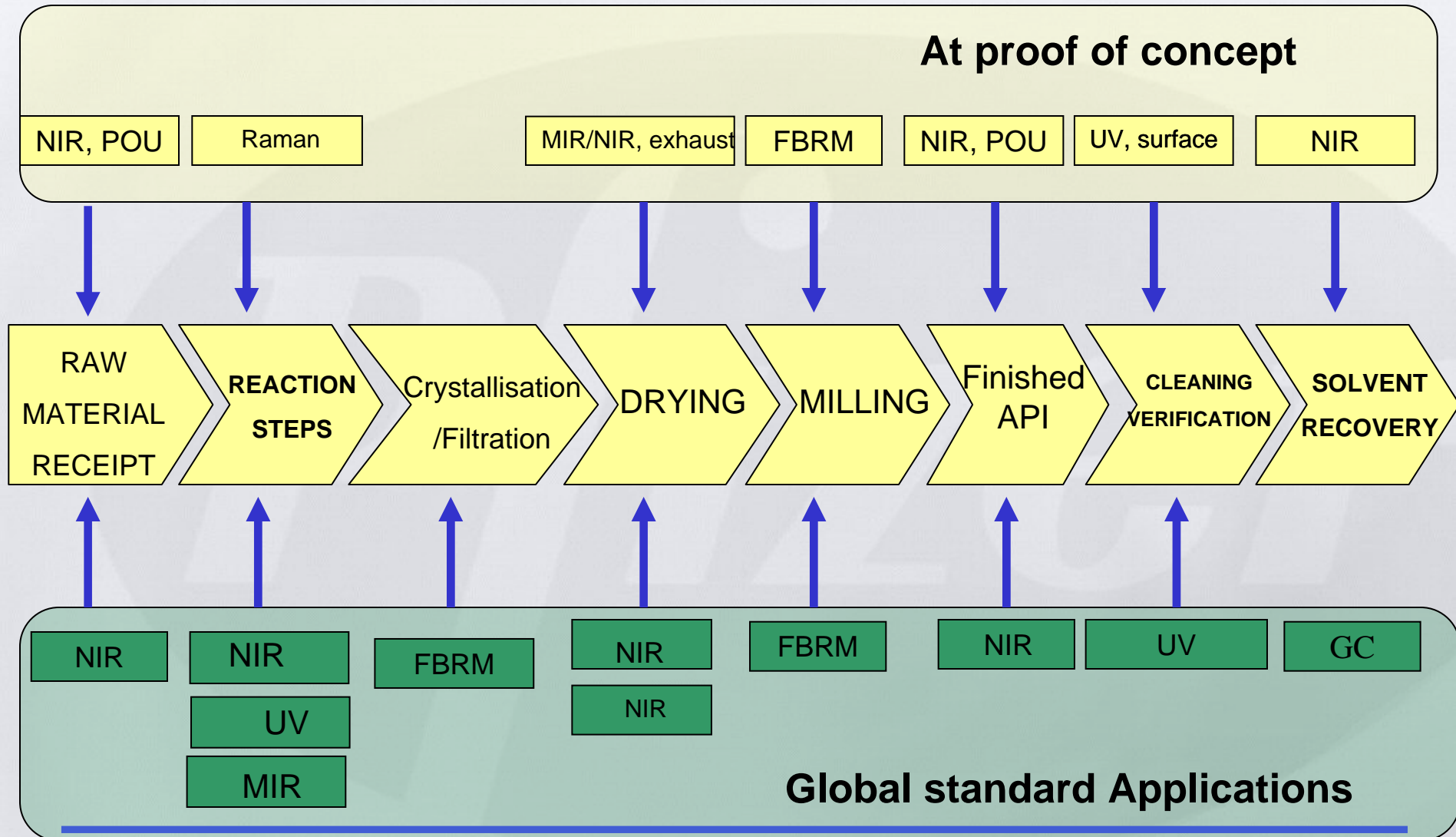


- *Risk based PAT projects priority list*
- *Focus on the voice of the customer*
- *Relentless focus on the process*
- *PAT applied where the need and benefit are greatest*
- *Focus on key quality attributes for new processes*
- *PAT enabling RFT manufacturing*

KEY AREAS OF PAT APPLICATION (API)



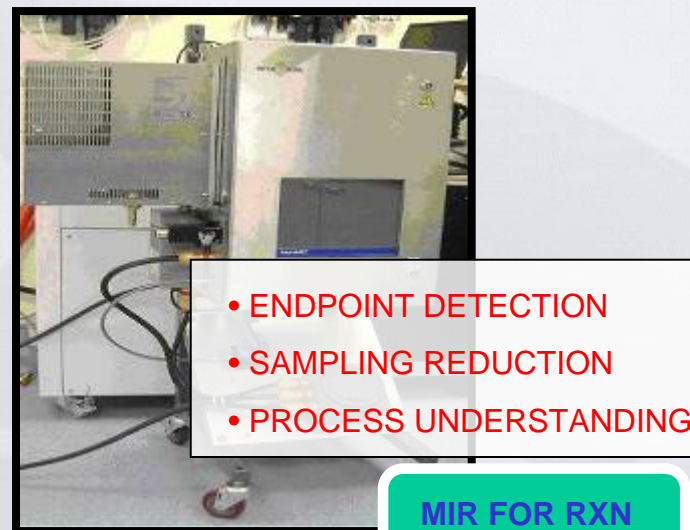
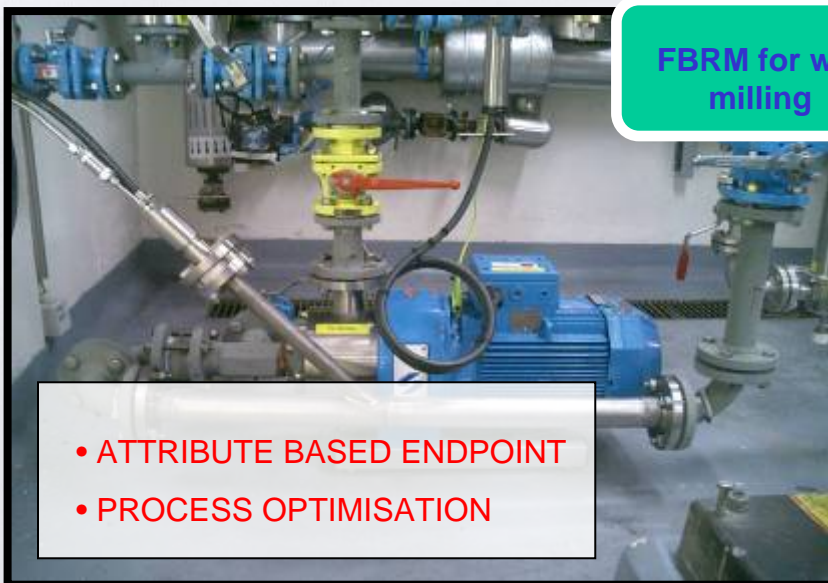
Application of PAT in Pfizer to support API manufacturing



PAT in action – API examples

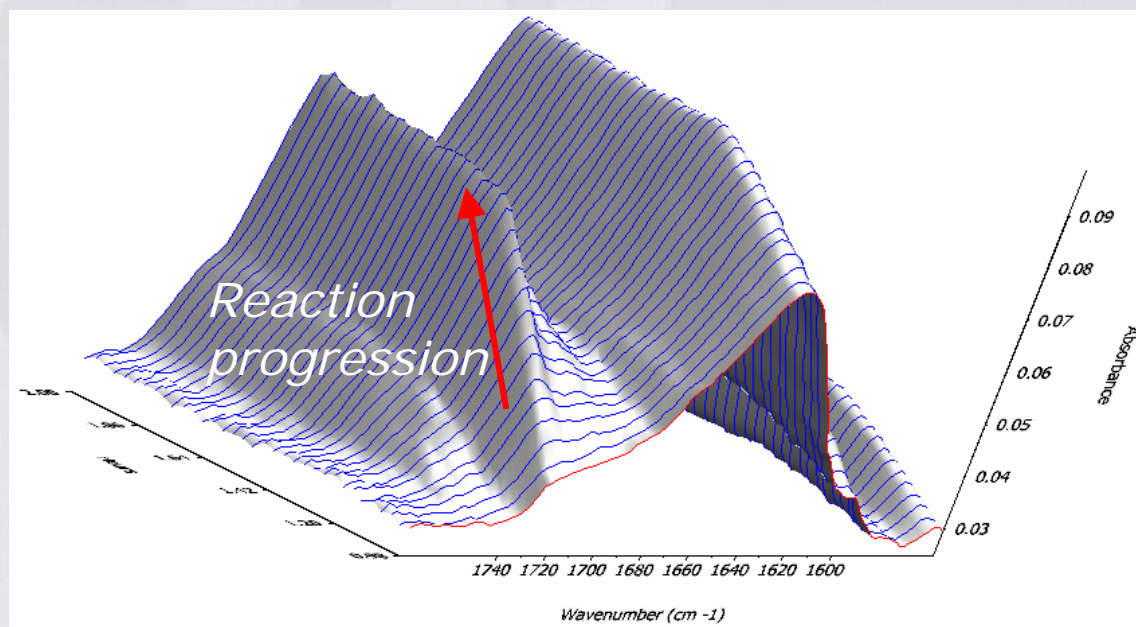


PAT in action – API examples



API case study

- New reaction route to API
- Level of reactant and impurities at RXN endpoint identified as key quality attributes
- Lab POC carried to demonstrate potential
- Qualitative model built on lab data



API case study



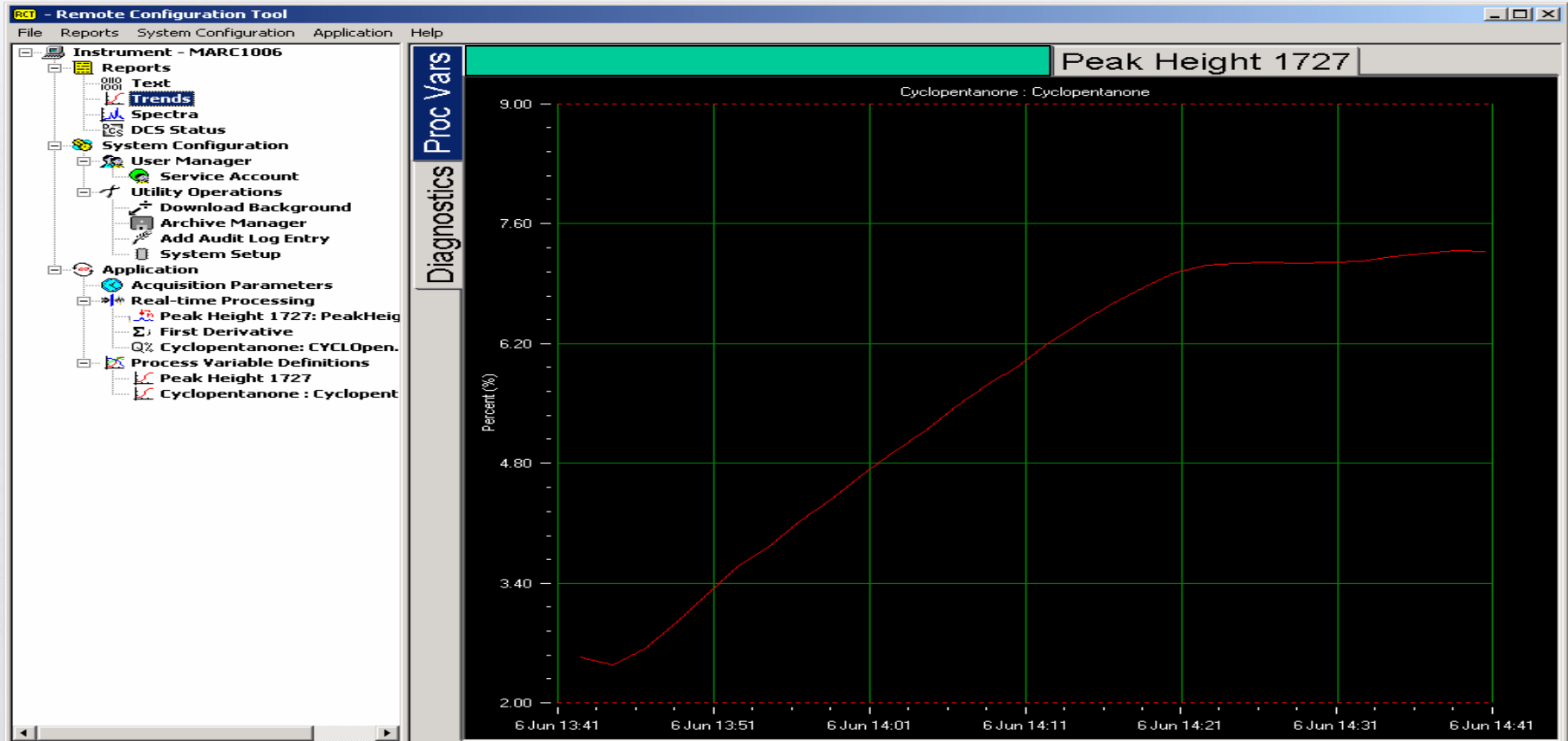
API case study



- MIR probe installed via recirculation loop

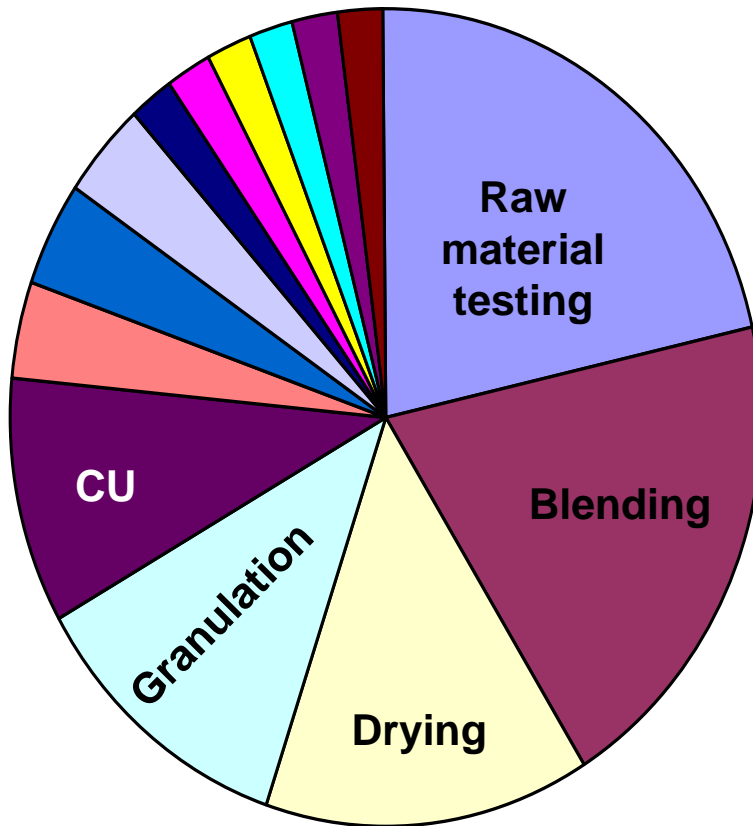


API case study



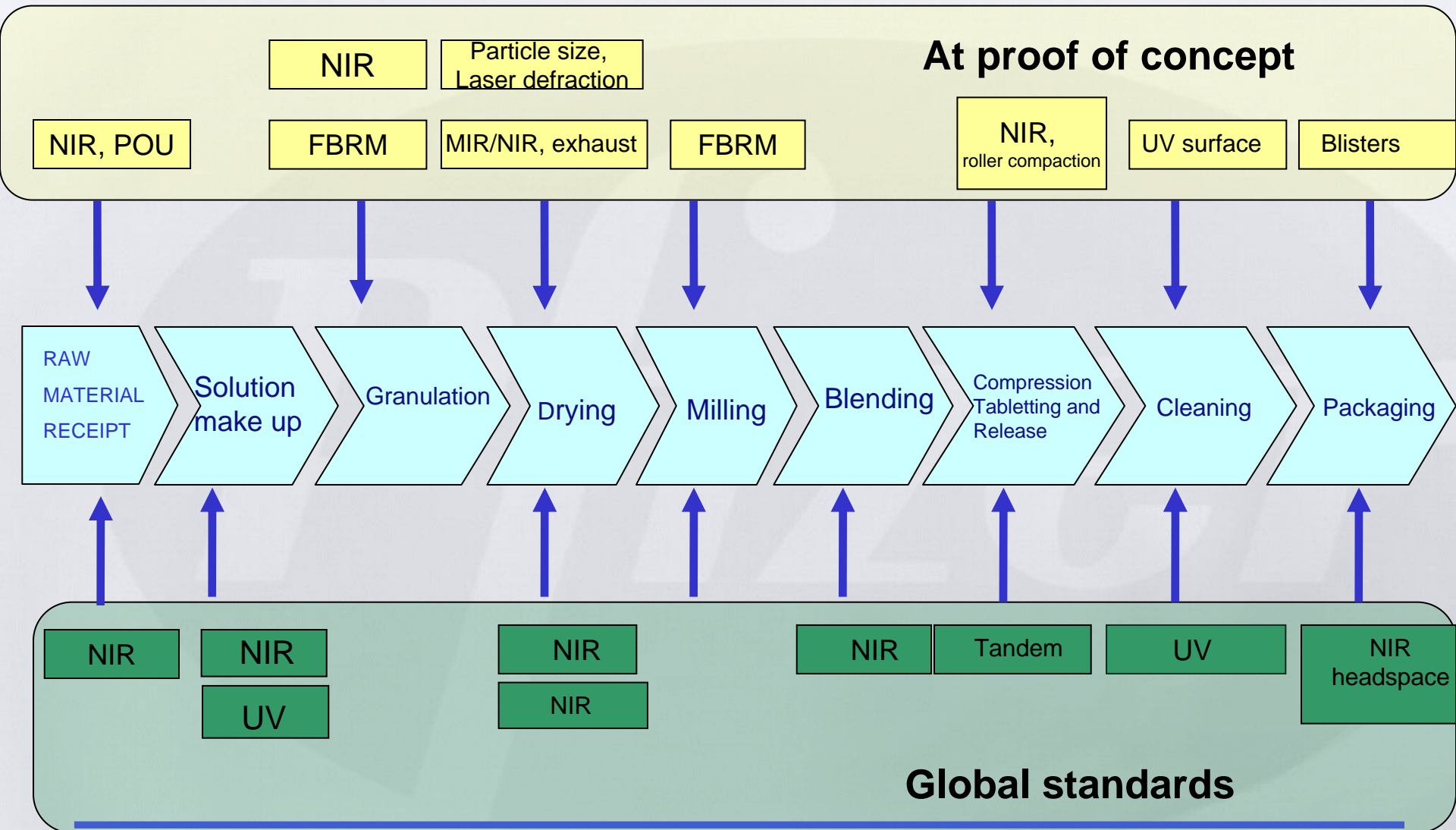
- Endpoint determined by MIR – attribute based endpoint
- Key addition point to reduce impurity formation identified by MIR
- PAT for rxn monitoring offers significant potential for variability reduction

KEY AREAS OF PAT APPLICATION (DP)

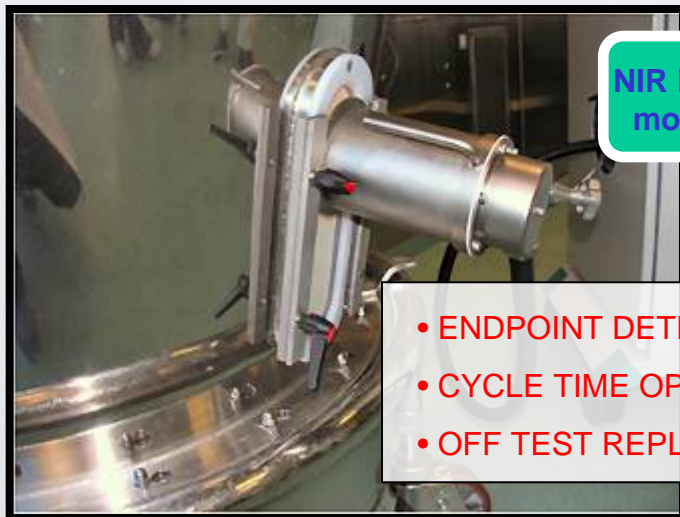


- Raw material testing
- Blend monitoring
- Fluid bed dryer monitoring
- Granulation monitoring
- Content uniformity and hardness of tablets
- NIR ID on finished products
- Roller compaction monitoring
- Vial headspace integrity monitoring
- Milling monitoring
- Cleaning verification/optimisation
- Rapid micro testing
- Particle size distribution in suspensions
- Vial content uniformity
- Solution concentration monitoring

Application of PAT in Pfizer to support DP manufacturing

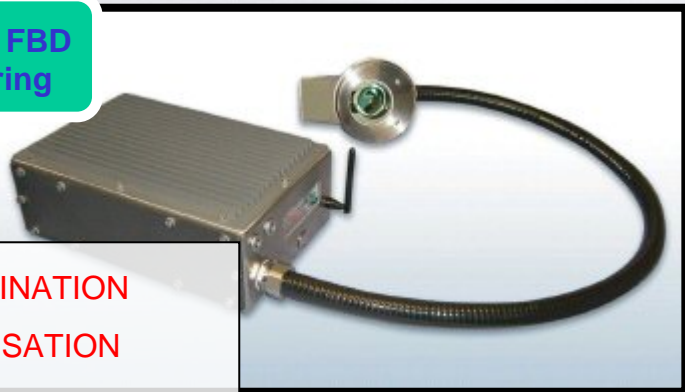


PAT in action – DP examples



NIR FOR FBD monitoring

- ENDPOINT DETERMINATION
- CYCLE TIME OPTIMISATION
- OFF TEST REPLACEMENT



NIR for blend monitoring

- BLEND PROCESS DEVELOPMENT
- BLEND PROCESS VALIDATION

MPA for raw material ID



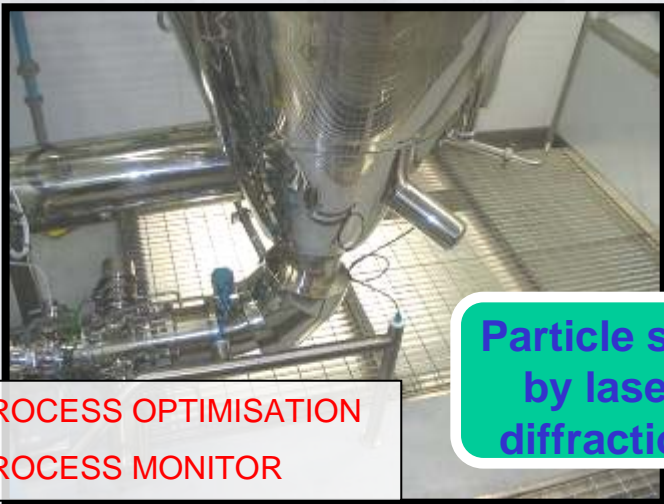
- Rapid raw material release
- Conformity testing

PAT in action – DP examples



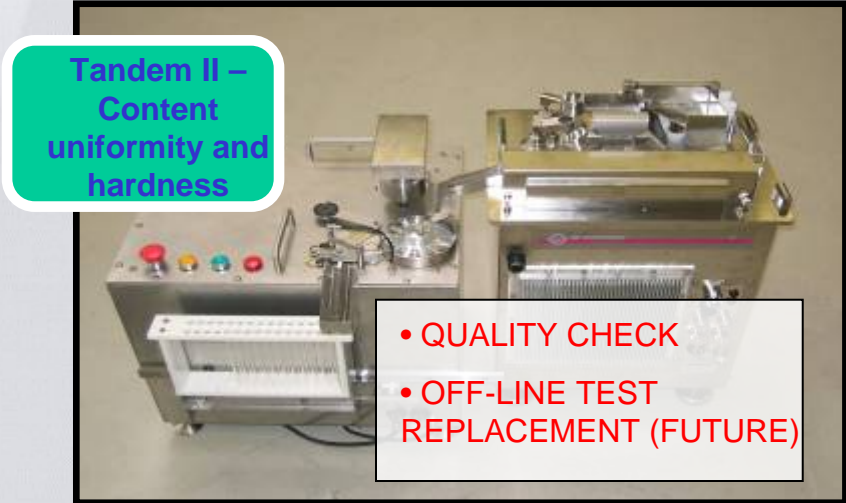
NIR for vial integrity

- QUALITY CHECK
- ROOT CAUSE ANALYSIS



Particle size by laser diffraction

- PROCESS OPTIMISATION
- PROCESS MONITOR



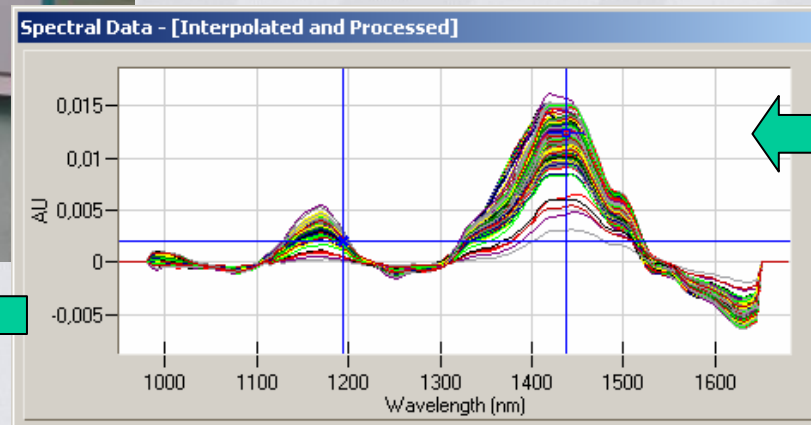
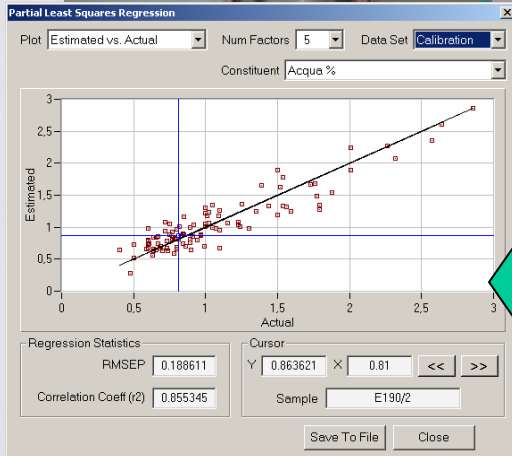
Tandem II – Content uniformity and hardness

- QUALITY CHECK
- OFF-LINE TEST REPLACEMENT (FUTURE)

Drug product case study



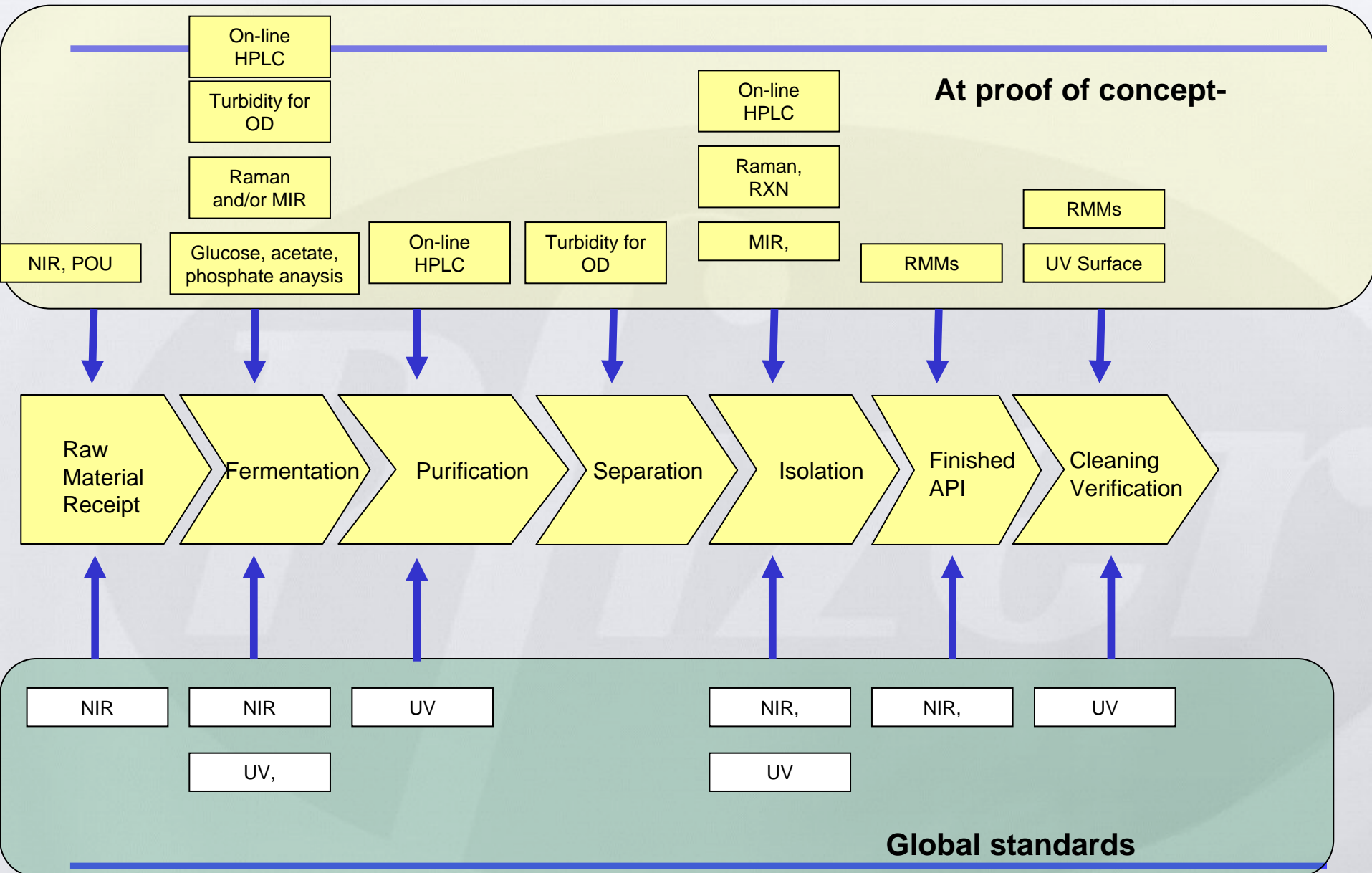
- NIR installed and qualified to track drying of finished product in fluid bed dryer
- Quantitative model build based on PLS correlation with off line samples
- Model validated through extensive testing
- Application submitted as part of EMEA worksharing review pilot



EMA worksharing process

- A method to monitor the drying of a drug product real time using NIR was submitted as part of the EMA 'worksharing' pilot.
- Pilot process used individual agencies to carry out a single review and provide recommendations for approval to other agencies. Aim is to significantly reduce review time.
- Classification (Type I vs Type II) debate illustrated difference of opinion between regulators on 'novel' status of NIR.
- Approval notification received April 2008

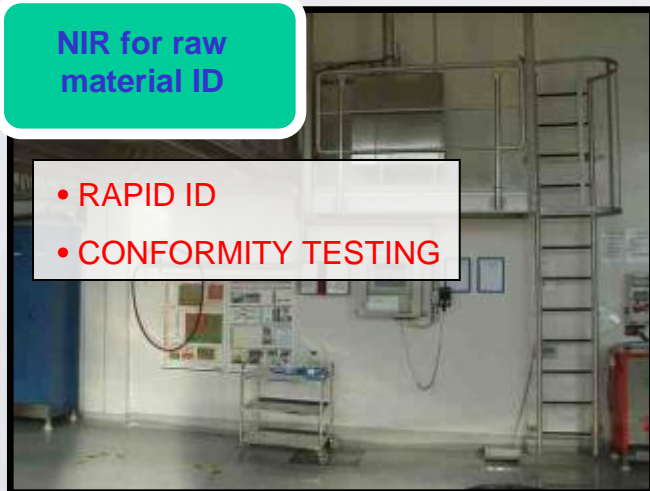
The role of PAT in PGM Bio API manufacturing



PAT in action – Bio examples

NIR for raw material ID

- RAPID ID
- CONFORMITY TESTING

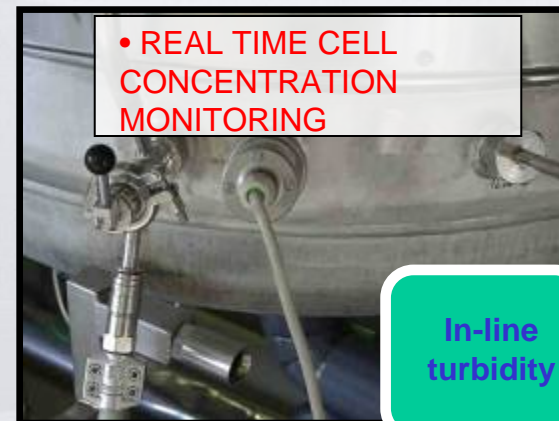


- REAL TIME CONTROL OF FEED



- REAL TIME CELL CONCENTRATION MONITORING

In-line turbidity



In-line glucose FIA

- FRACTION DETECTION
- ON LINE IMPURITY CHECK

In-line HPLC



- DISTILLATION MONITORING AND CONTROL

Ultrasonic monitoring of distillation



Pictures courtesy of Thomas Krumm, Frankfurt

Benefits and challenges of PAT

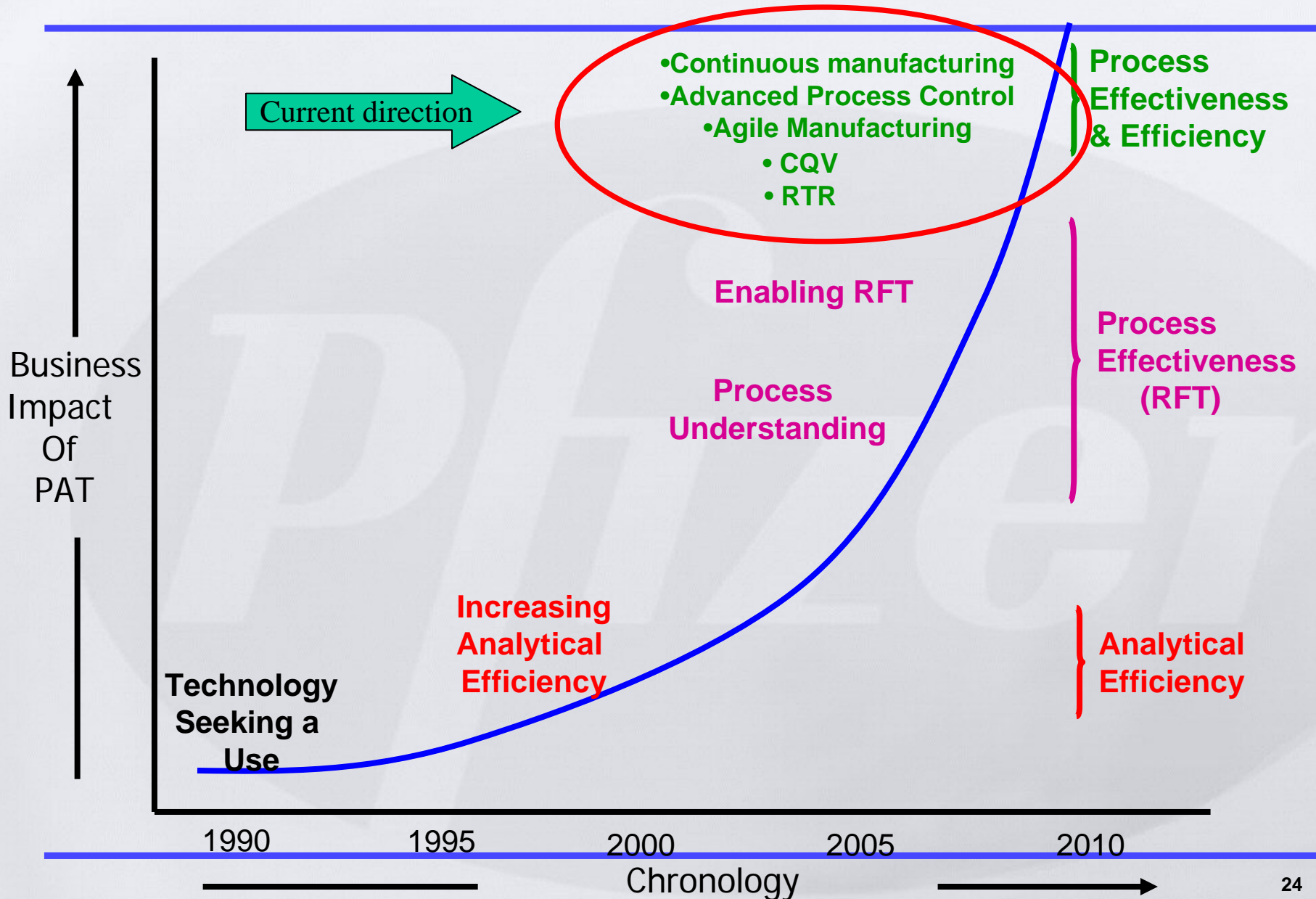
■ Benefits

- Real time window on process
- Root cause determination
- Increase in process knowledge and understanding
- Ability to reduce process variability
- Sampling, testing, product contact reduction
- Attribute based endpoints
- Process control
- More agile manufacturing operations

■ Challenges

- Technology robustness
- Cost
- New skill sets needed across functions
- Reluctance for change
- Perception of regulatory obstacles

Future direction for PAT at Pfizer



Future direction of PAT at Pfizer

- **A number of pilots are already underway focussing on new manufacturing paradigms**
 - **Continuous processing**
 - **Continuous quality verification**
 - **Real time release**
 - **Advanced process control**
- **PAT is an important enabler for these pilots**
- **Close interaction and discussion with regulators will be essential**

Acknowledgements

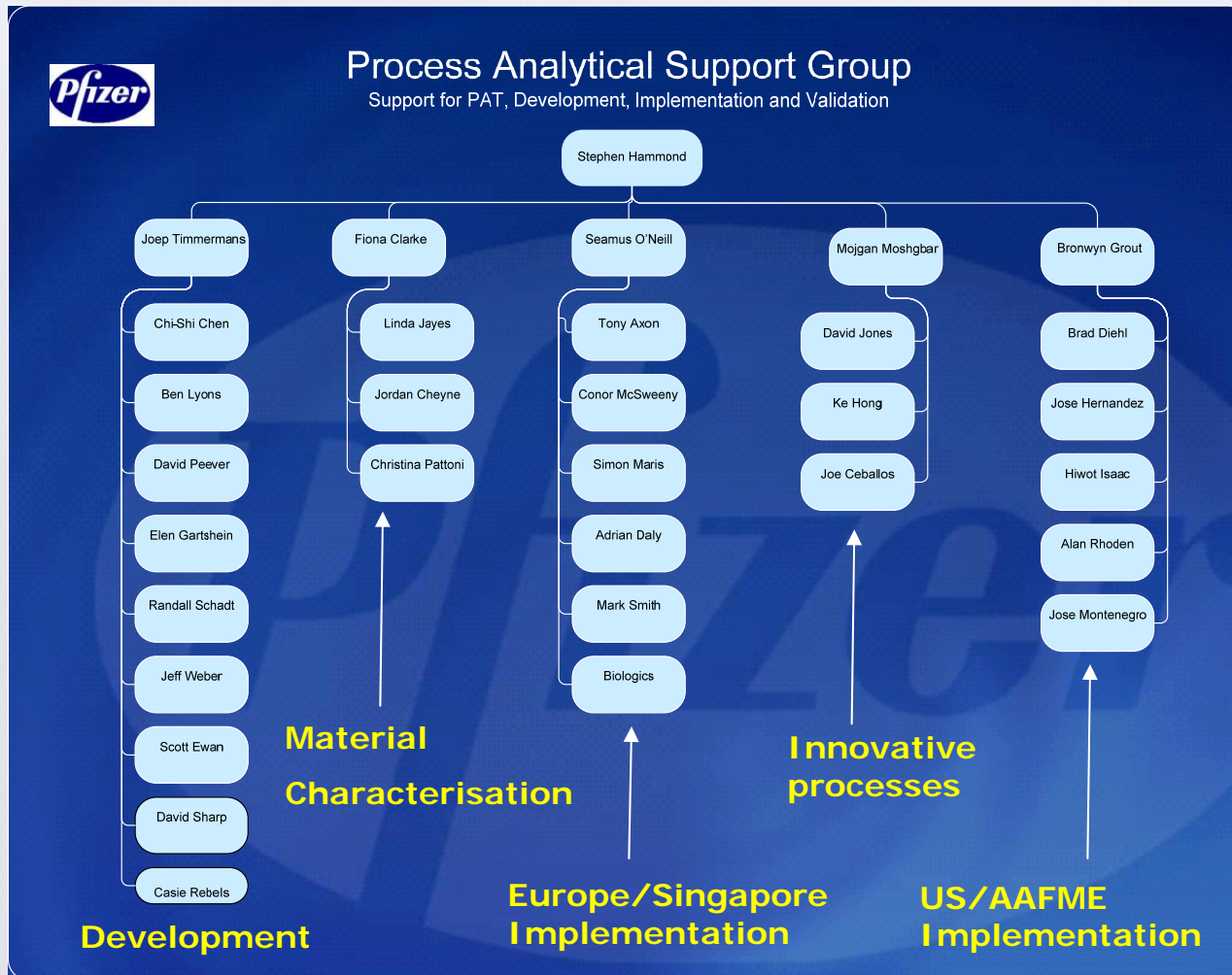
- **Rossana Della Ventura, Ascoli**
- **Adrian Daly – PASG**
- **Tony Axon - PASG**
- **Thomas Krumm - Frankfurt**
- **Pat McGauley - Little Island**

BACKUP

Pfizer

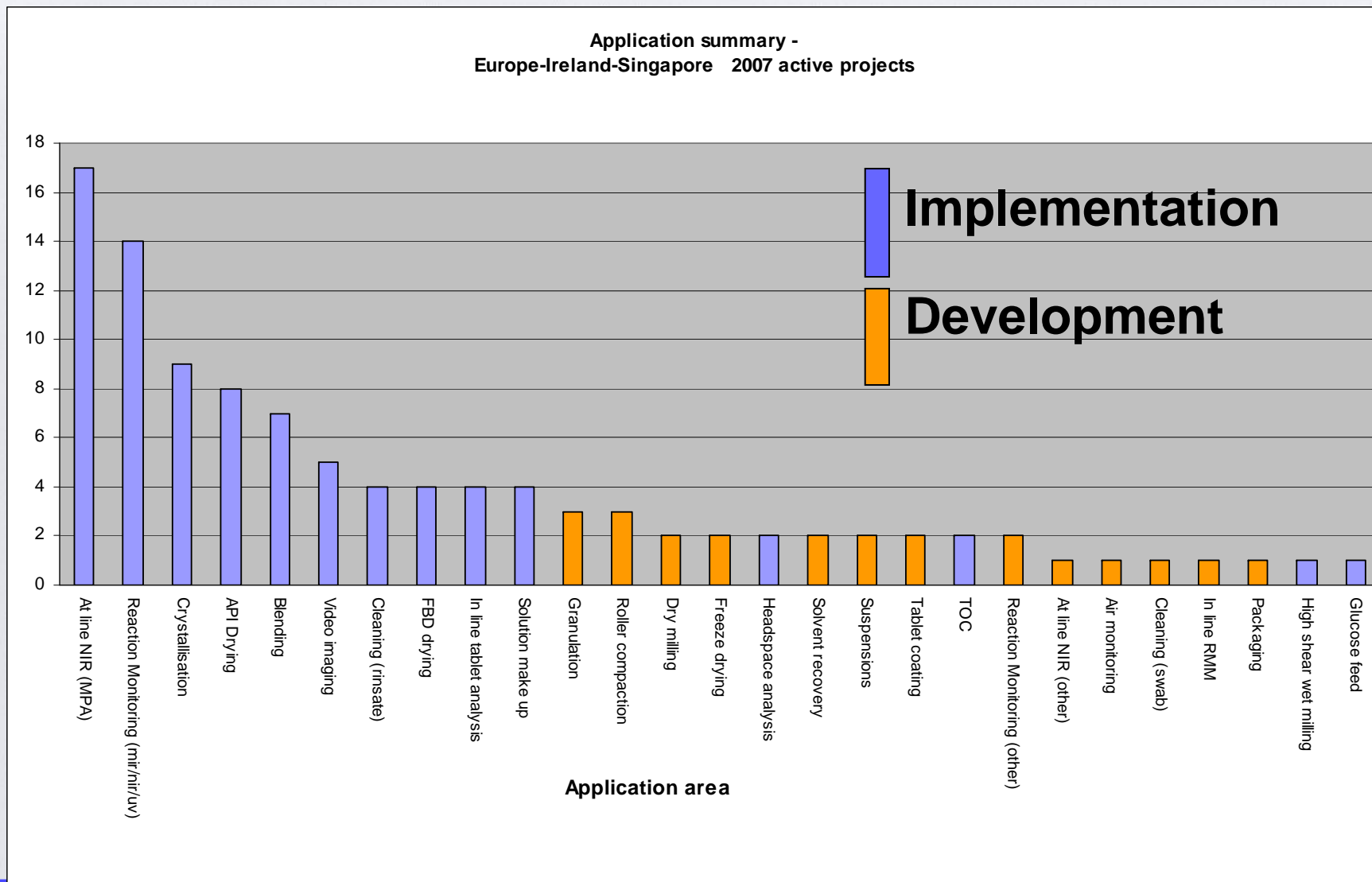
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- *CQV: An approach to process validation where the manufacturing process performance is continuously monitored, evaluated and adjusted (as necessary). A science based approach to verify that the process is capable and will consistently produce product meeting predetermined quality attributes*
 - *RTR: An outcome of a control strategy in which product quality is assured for batch release through a combination of process information and input or in-process material attribute measurements during manufacturing in lieu of traditional off-line, end product testing.*
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Support structure for PAT in PGM

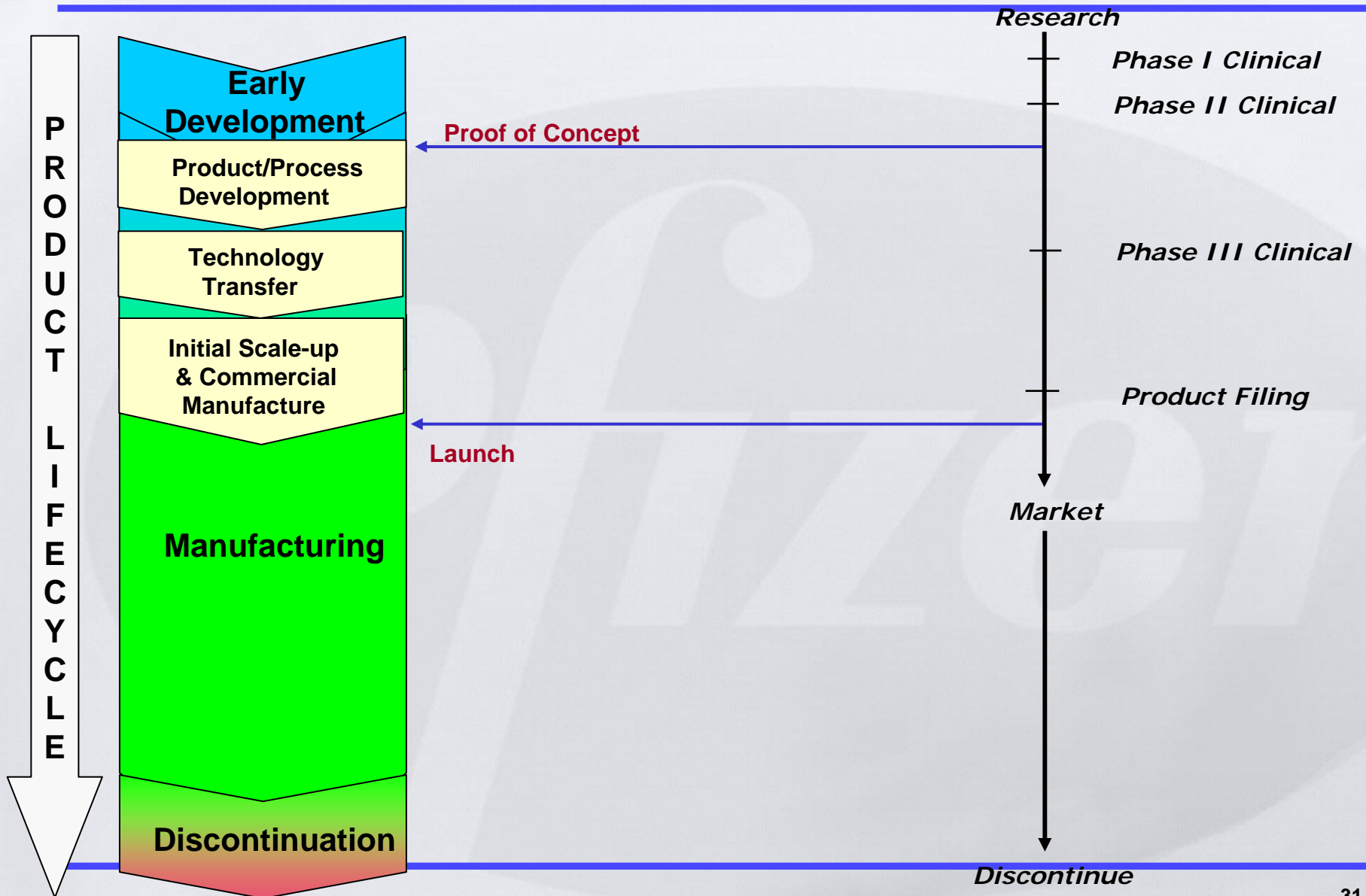


- **Global PAT support team**
- **Technology development and evaluation**
- **PAT implementation**
- **Innovative pilots**
- **Material characterisation**
- **Active sites have dedicated PAT leads/teams**
- **PASG works closely with site PAT leads**

Application spread – Europe/Ireland-Singapore 2007



Pfizer Quality System



Monitoring in Development and Co-Development

