In-line analysis (PAT) in drug substance development

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Reaction Monitoring using NMR and Vibrational Spectroscopy
Sandwich 22nd March, 2011

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Use of in-line analysis in Drug Substance Process Development

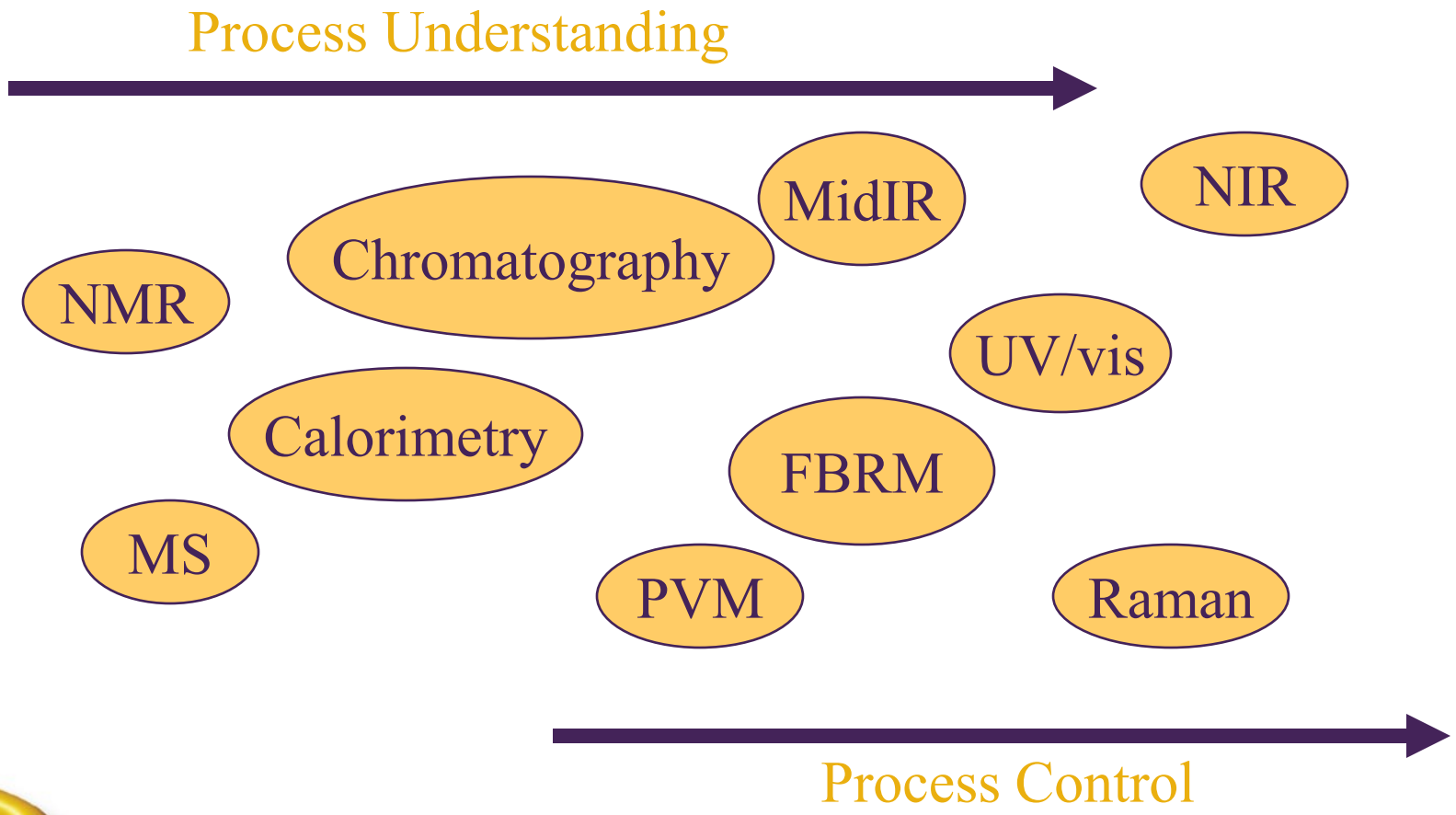
Background

- Applications in AZ chemistry labs from mid 1990's
  - Predominantly using midIR
  - Single use of NIR in Pilot Plant (Swedish project)
- Demand for "difficult to monitor" processes in lab
  - Poor uptake because no capability at scale
- From 2002 developed and implemented strategy for in-line monitoring (…which we called PAT)
  - Focus on midIR, NIR, Raman, UV/vis, Lasentec FBRM
  - Using in-line analysis as an "eye" in processes
- Seen increased use in labs and Pilot Plant

In-line analysis in Drug Substance Process Development, AZ

- Drivers for using in development
  - Increase process understanding
    - Use information to help develop robust processes and using the knowledge to define design space
  - Increase processing efficiency
  - Shorten lead times
- Process analysis can have a different impact at different stages of development
  - From Route design to Design Space Finalisation/Control Strategy
- Range analytical techniques can be used
  - PAT can be in/on/at/off-line

PAT Techniques and Scale



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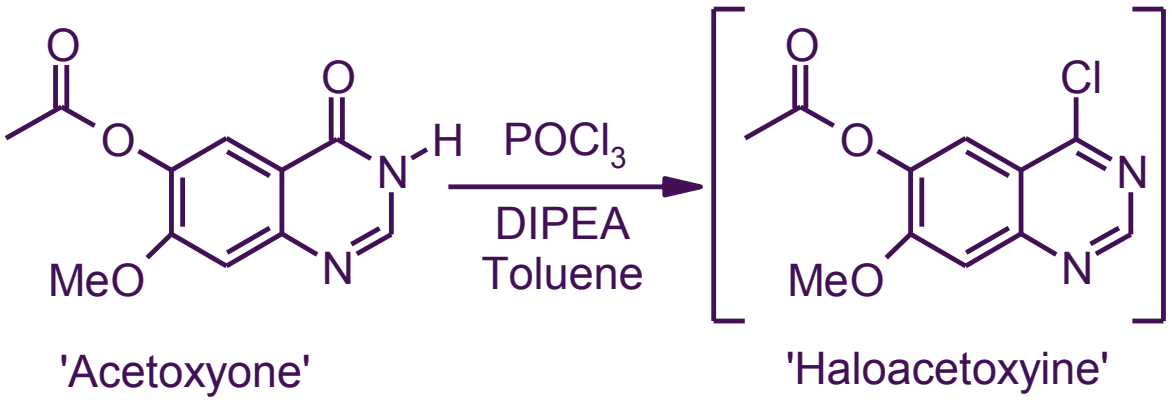
Benefits of using in-line analysis

- Real-time data
  - Facilitate process understanding / product quality
  - Increase processing efficiency
  - Process optimisation on scale-up / troubleshooting
  - Opportunity for process control / real-time release
    - Monitoring continuous processes
- Sampling
  - Increased reproducibility
  - Minimise exposure to hazardous reagents
- Suited for process monitoring of:-
  - Heterogeneous reactions
  - Air/moisture sensitive reactions e.g. lithiation reactions
  - Cryogenic reactions
  - Pressure reactions e.g. hydrogenations
  - Vacuum distillations

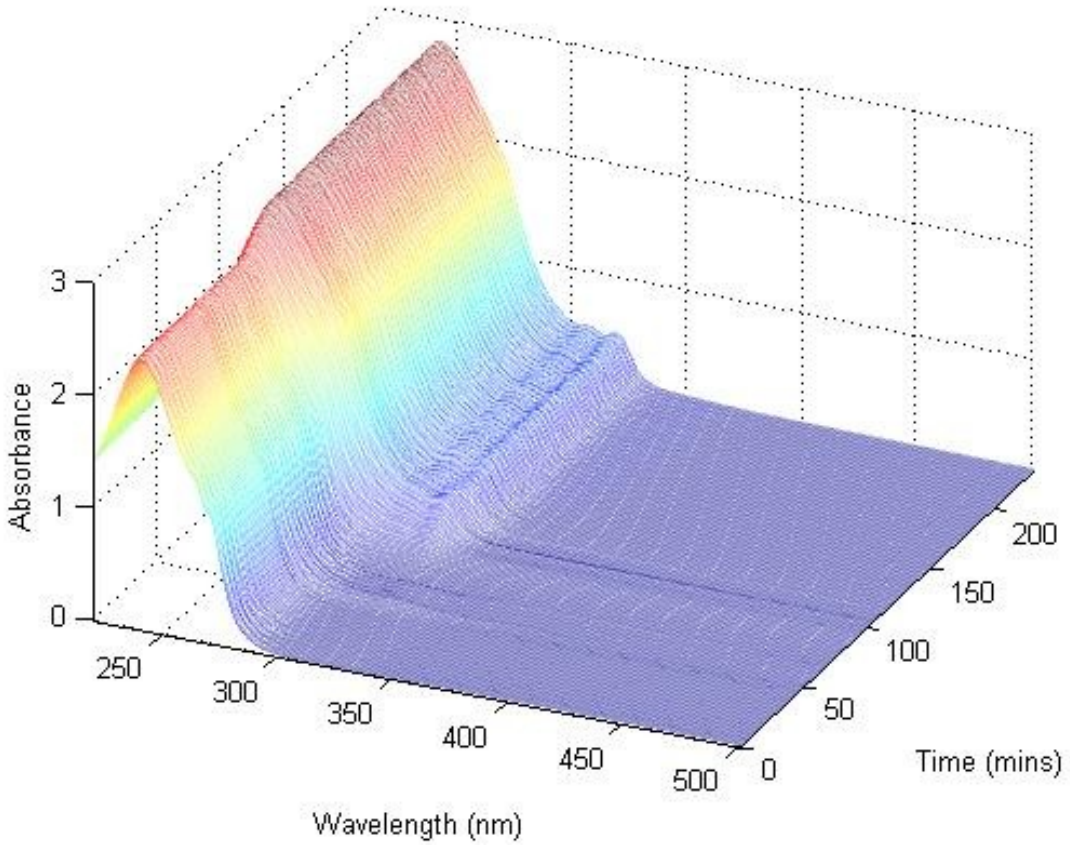
Heterogeneous (Chlorination) Reaction



'Acetoxyone' 'Haloacetoxyine'

- Can this chemistry be monitored using in-line spectroscopy?
- The reaction mixture starts as a slurry. The starting material (acetoxyone) has poor solubility but dissolves during the course of the reaction
- Taking quantitative reaction samples is difficult as solute precipitates out as the sample cools down a few degrees

Data acquired by in-situ UV-ATR Spectroscopy



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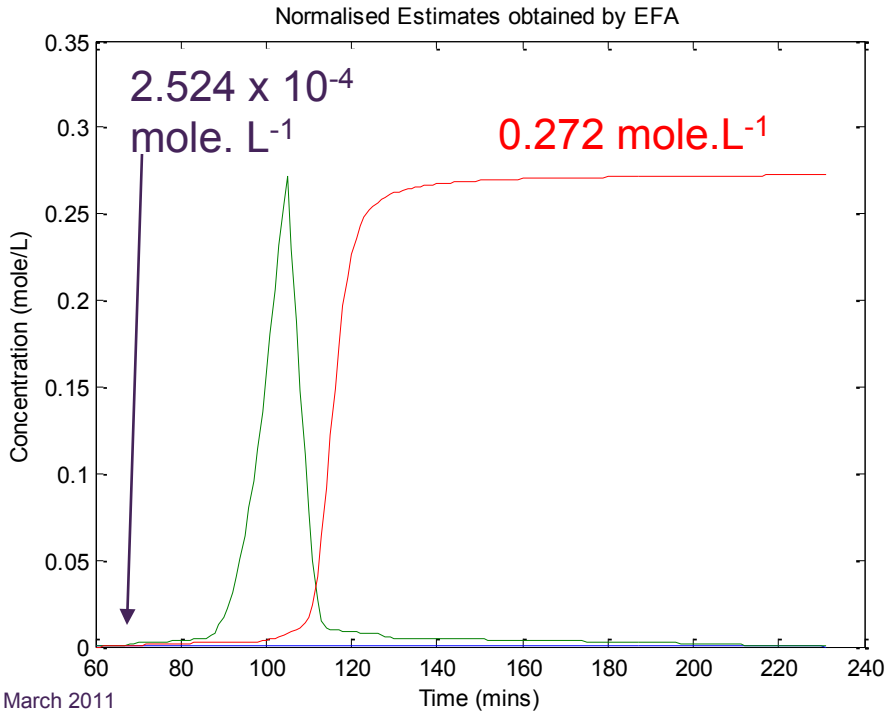
Developed PLS Calibration Model

- Evolving Factor Analysis was used to get an approximation of the concentration profiles
- Knowledge of limited solubility of acetoxyone (2.524×10^{-4} mole. L^{-1}) and haloacetoxyine solubility at EOR (0.272 mole.L^{-1}) allows crude profiles to be scaled
- Further chemometric analysis (curve resolution techniques) enabled refined estimates of the starting material, intermediate and product concentration profiles to build a PLS calibration model



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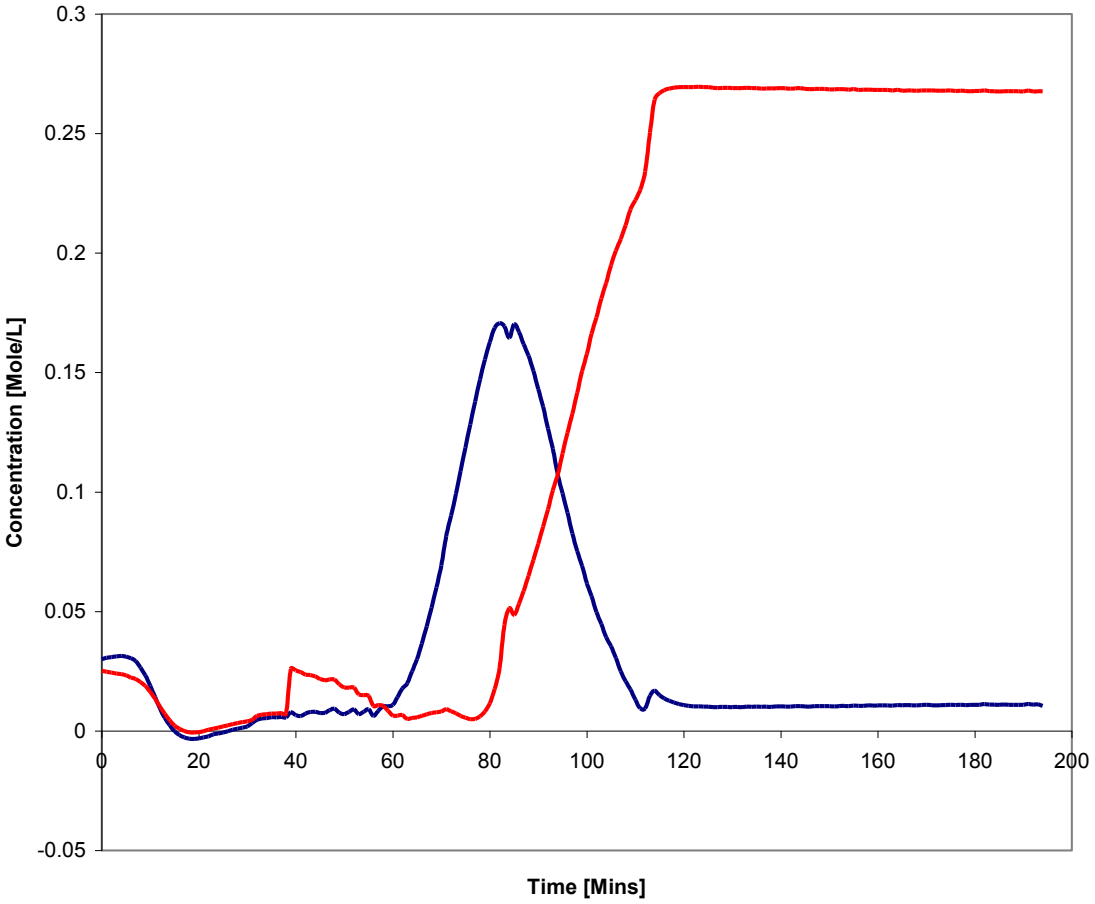
Results from LSL Batch 1



Based on charges, the theoretical EOR concentration of product should be 0.275 mole/L

HPLC sample (based on peak areas) confirmed amount of starting material remaining <0.5%

Ref: N Pedge and T Walmsley, App.Spectr., 61 (9), 949, 2007

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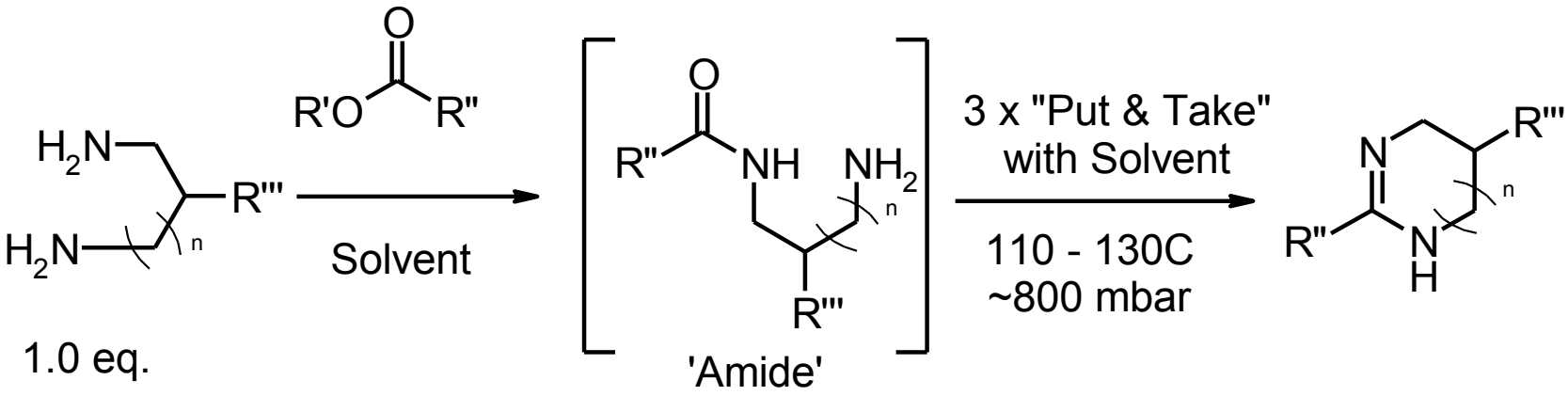
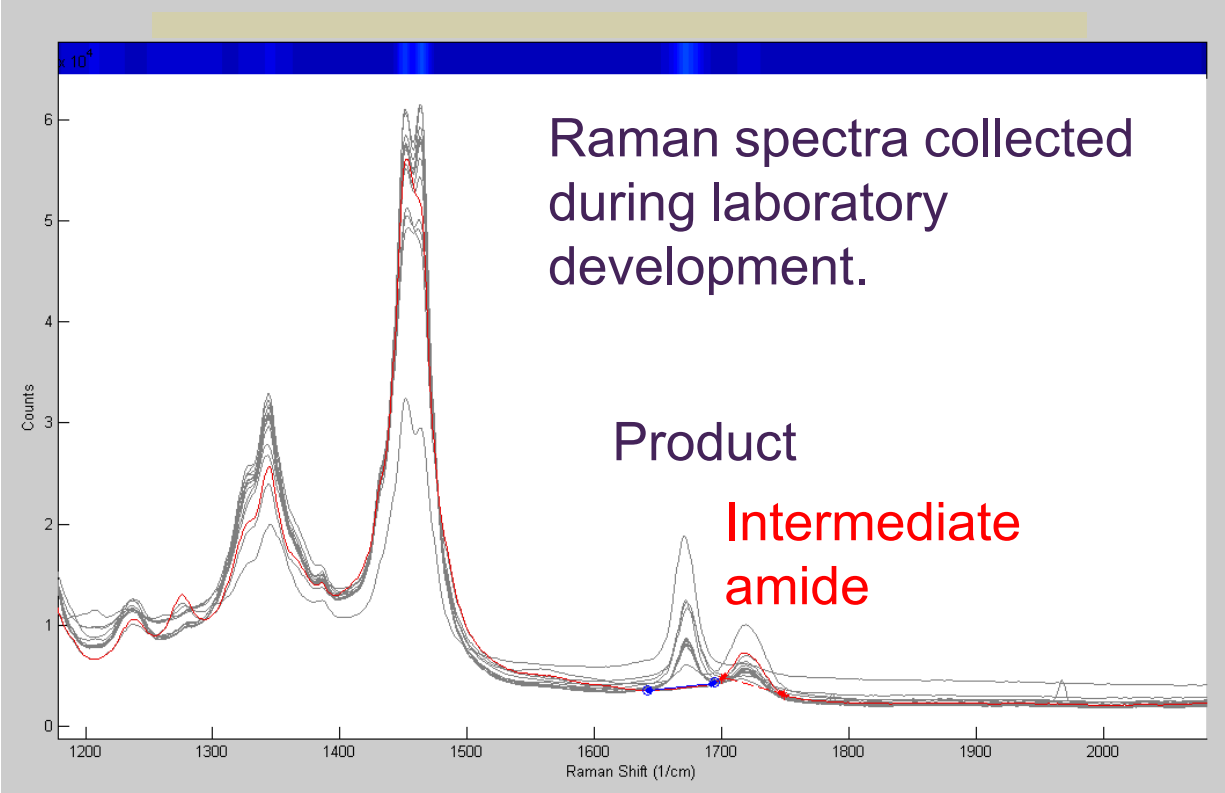
Monitoring a cyclisation reaction using Raman



- Formation of the amide intermediate is rapid (<5 mins)
- Conversion to product was achieved using 3 “put & take” distillation cycles to remove water and drive reaction to completion
  - Rate of conversion sensitive to temperature
  - Used high b.pt solvent also sensitive to pressure

Monitoring a cyclisation reaction using Raman

- During the 3 ‘put-and-take’ cycles, extent of conversion would be unknown.
  - Sampling for off-line analysis would require breaking vacuum and allowing the vessel to cool
- The use of an *in-situ* spectroscopic method to monitor the conversion was considered.
- Off-line GC analysis (reference data) was available to correlate spectral measurements and build model
  - The reaction mixture is homogeneous so obtaining representative samples was not an issue.



- Raman spectra show good selectivity for both the amide intermediate and the cyclised product.
- Only baseline correction and spectral normalisation required.
- Linear regression transformed Raman peak ratio into GC peak ratio using samples after each “put-and-take”. IPC limit 95/5 % area = 19:1

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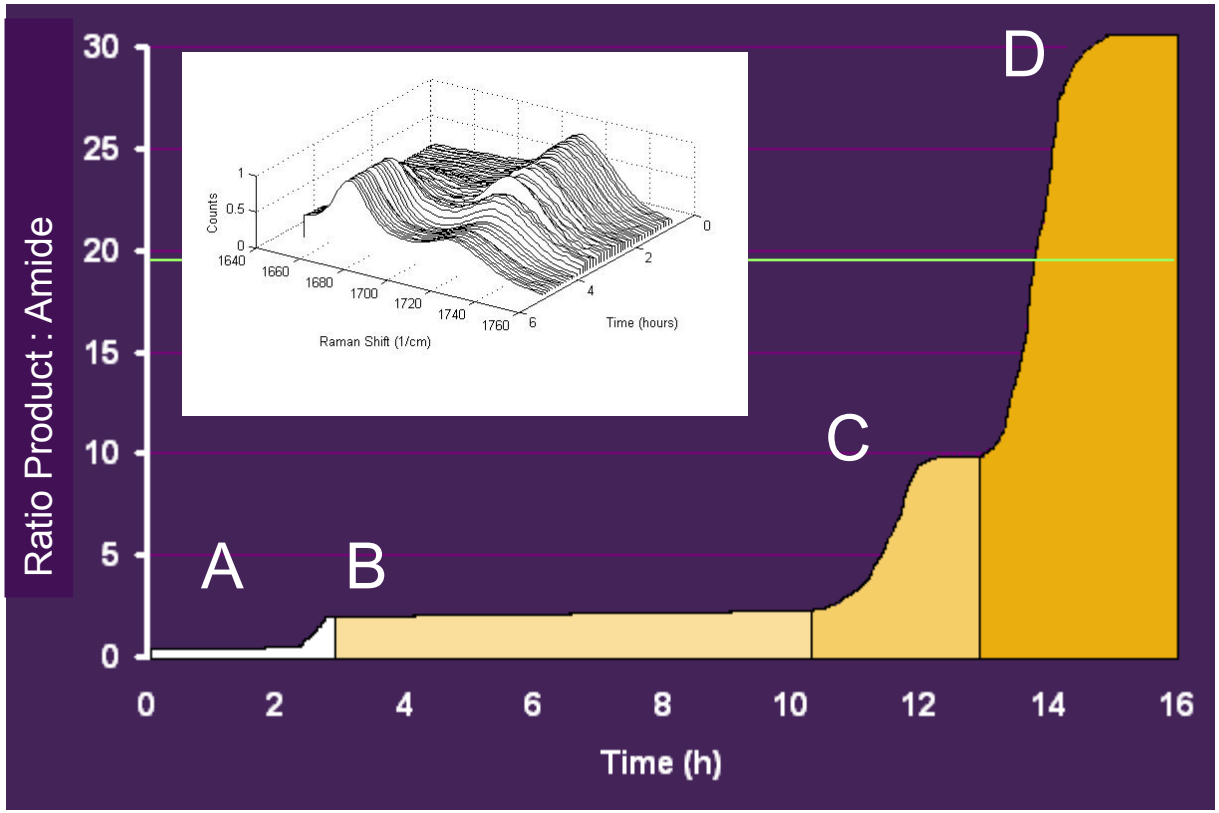

- In-line Raman gave us early warning of poor rate of conversion.
- Maintaining ~800 mbar proved very difficult in the pilot plant.
- Based on Raman, we decided to distil at atmospheric pressure.
- When sampled for off-line analysis, the end-of-reaction criterion was met (>95% product)

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Facilitating the use of in-line analysis in R&D

- Variety of applications and projects in R&D
  - Can we justify capital projects for new technology on case by case basis?
  - Not ideal for individual AZ projects from timing and cost perspective
- Strategic PAT investment (2002)
  - Designed as plug and play approach
  - Flex
  - Ra
    FE
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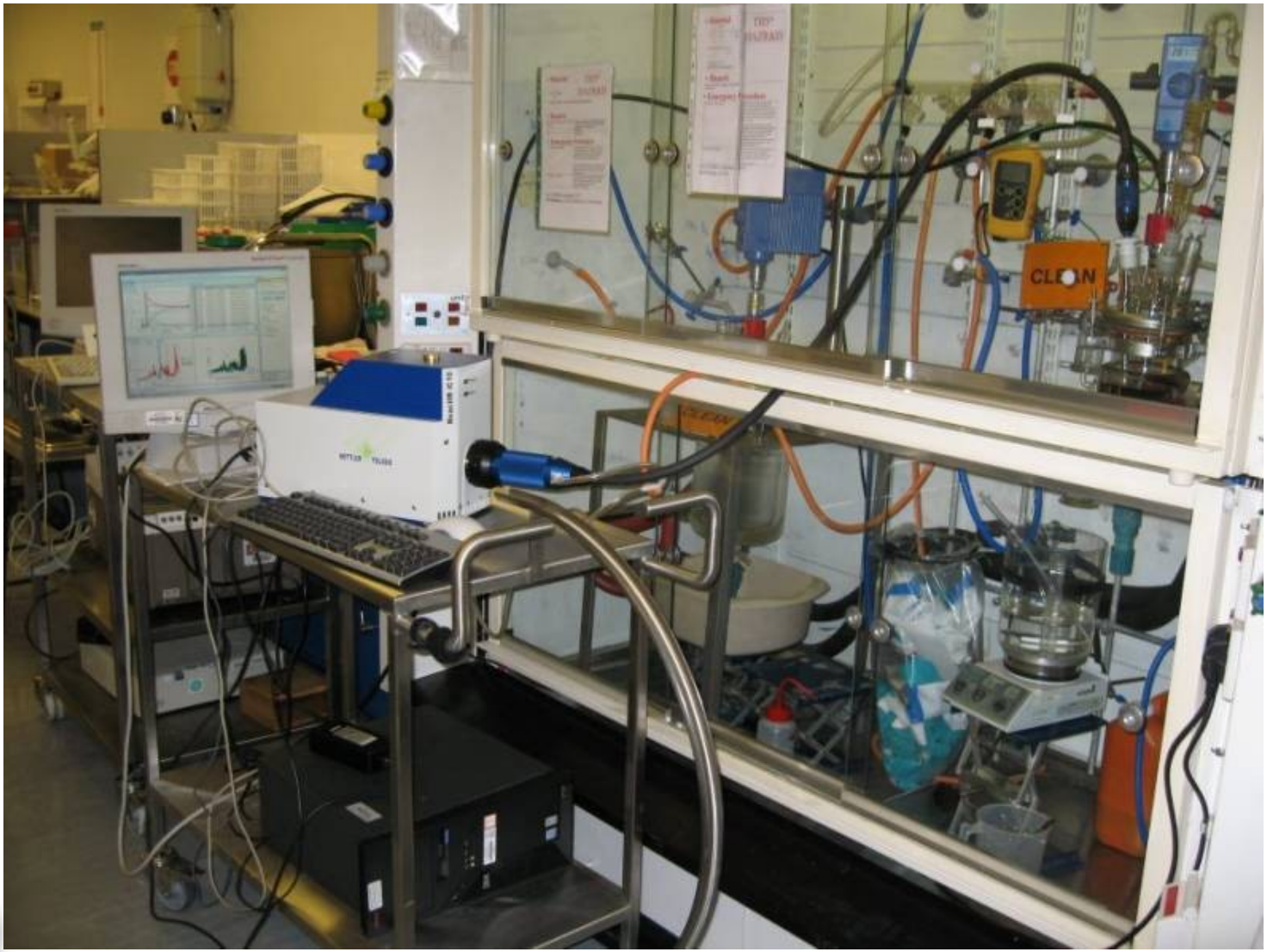
  - lity

- Total transformations in our development manufacturing group
  - 2007 – 14
  - 2008 – 23
  - 2009 – 33

Typical Laboratory set-up



Pilot Plant

- 12 reactors
  - -1 to 50 barg
  - -80 to +300 ºC
  - 0.125 to 2.5 m^3
  - GLMS or Hastelloy C22
  - Generally Zone 2 IIB T3
  - 2 areas Zone 2 IIC T5
  - Integral PAT port
- Gas addition e.g. hydrogenation, chlorination
- Highly reactives, DiBAL, BuLi

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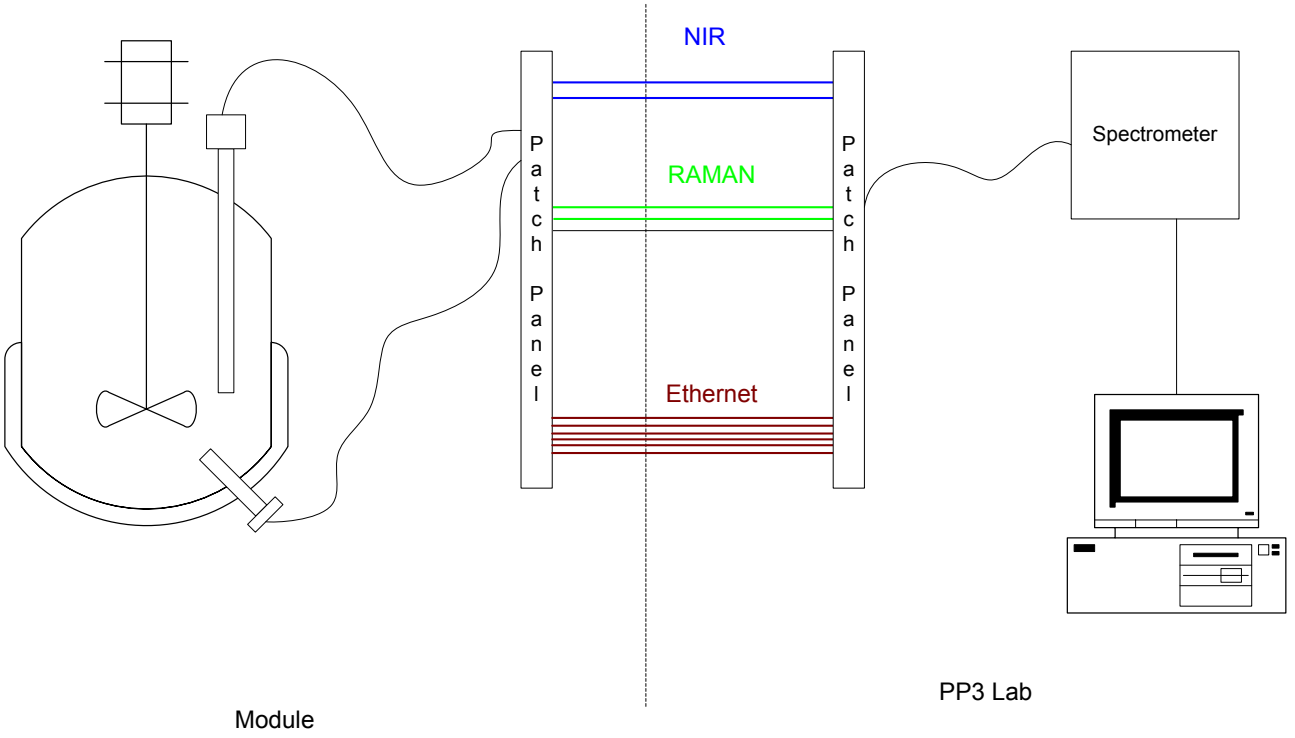
Large scale Laboratory (LSL)

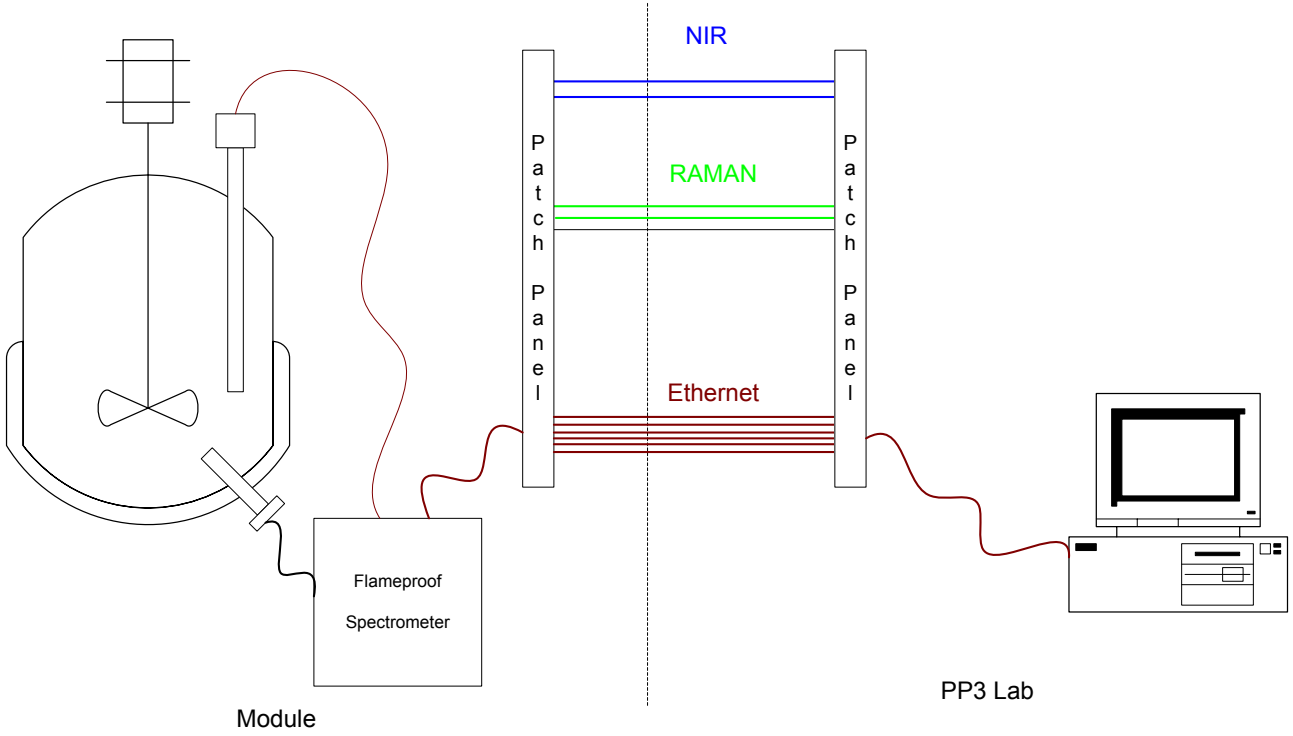
- Eight 25L & 50L GLMS/GLSS reactor systems in individual fume cupboards.
- 6barg Hydrogenator
- Rotary evaporator
- Mobile filters
- Manufacture 0.5 – 5.0 kg batch size
- Interchangeable agitators
- PAT probes inserted from above through the vessel manifold

NIR/Raman set-up



Raman or NIR

Explosion proof spectrometer set-up



UV/Vis, Lasentec (FTIR)

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Probe in reactor

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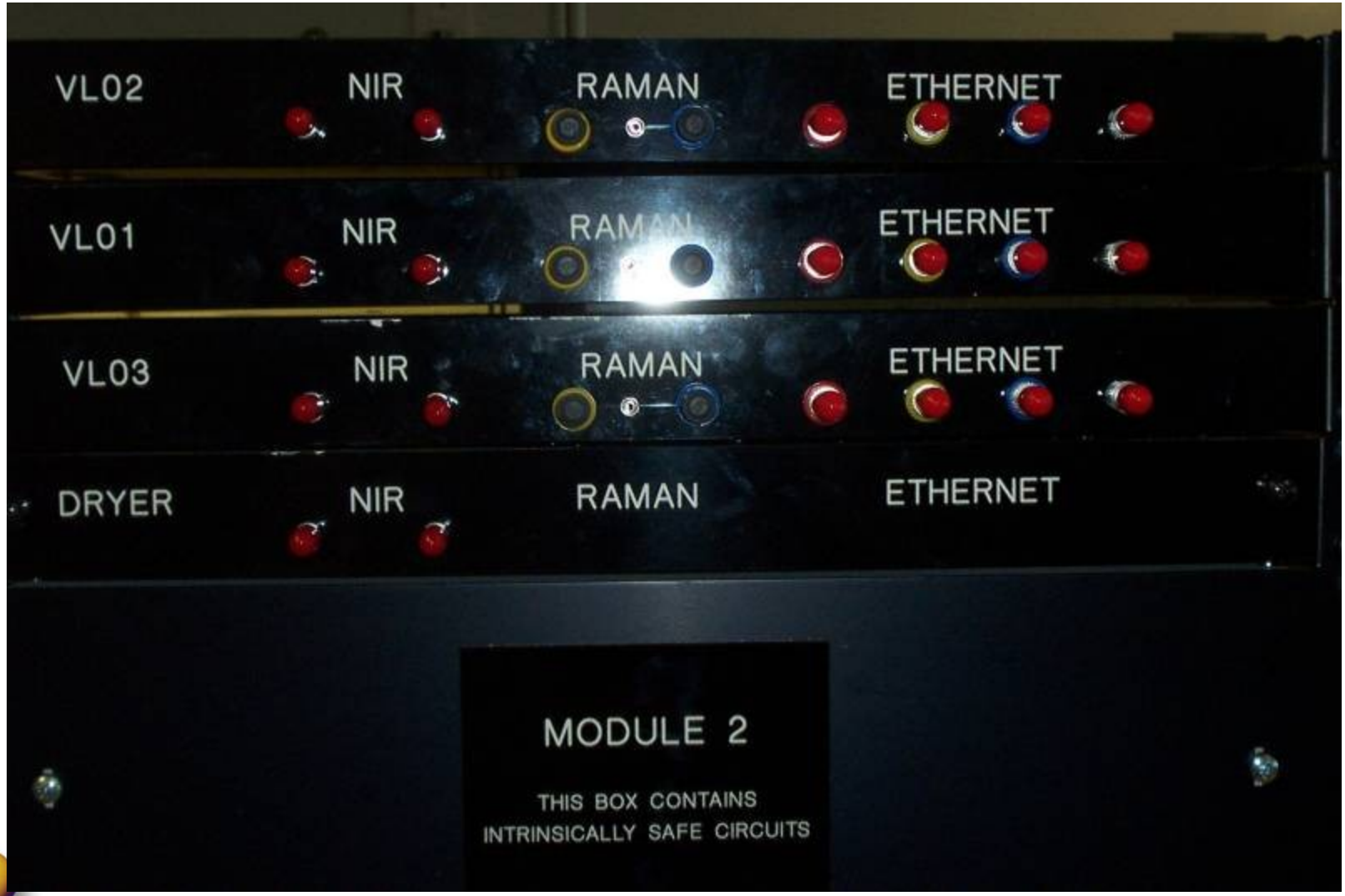
Laboratory patch panel



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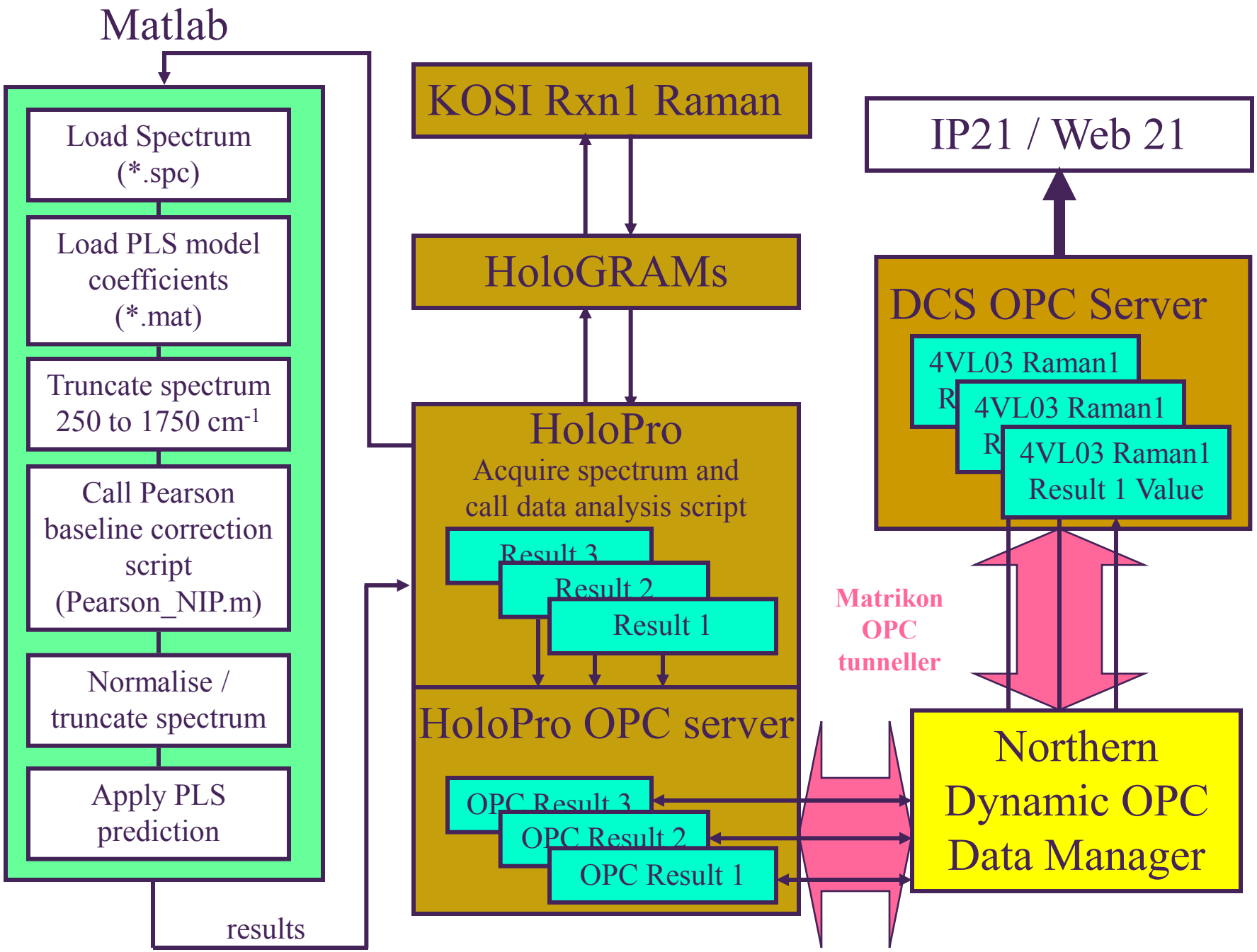
In-line analysis with Feedback control - “True PAT”

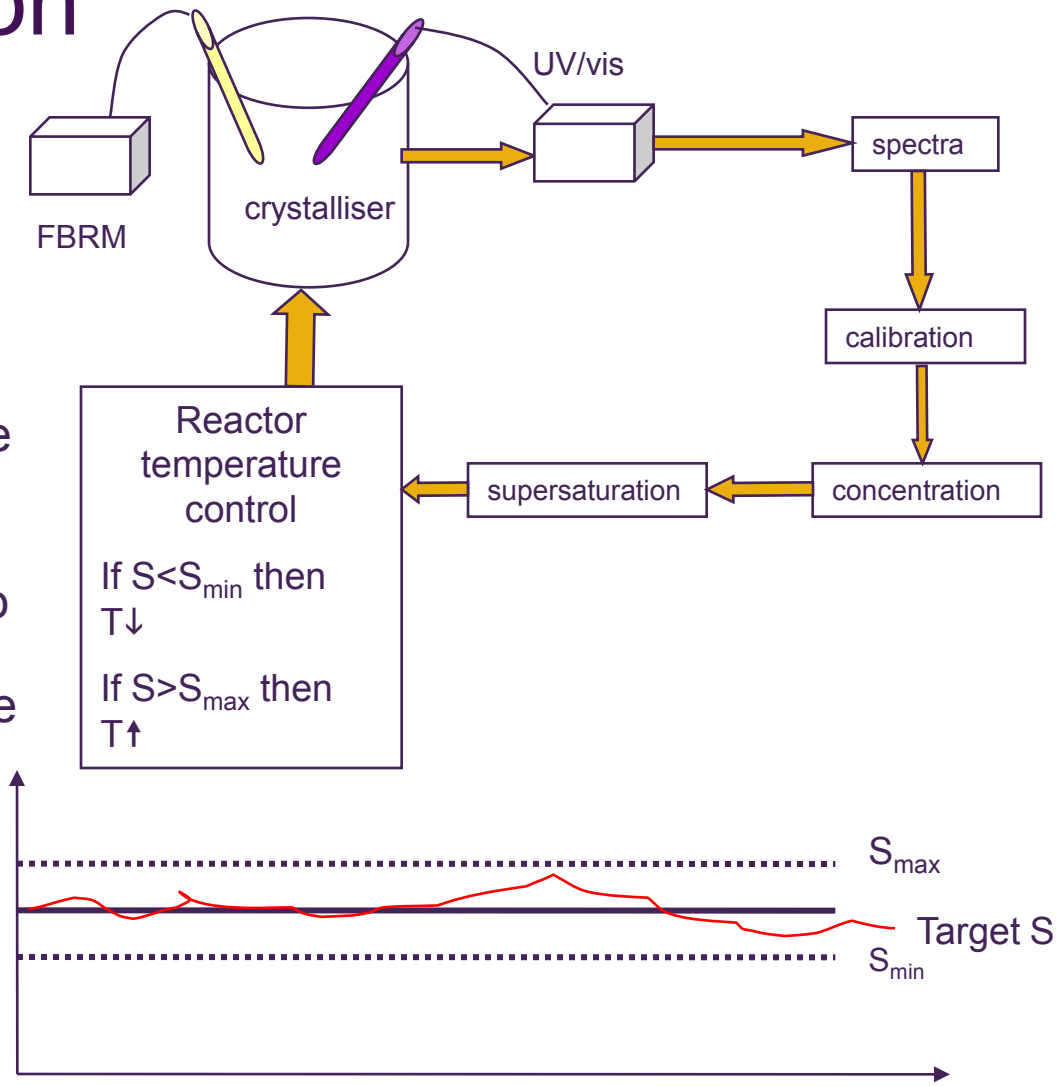
- Established communication between spectrometers and DCS of automated Pilot Plant
  - Using OPC servers
  - Allows information on chemical composition to be built into batch recipes
- With good knowledge of chemistry we can develop robust and efficient processes
- Deliver consistent product quality
- Example of feedback control
  - Crystallisation – Supersaturation feedback control



22nd March 2011

Closed Loop Feedback Control of Supersaturation

- In batch crystallisation, usually the feedback controller is designed to follow a pre-determined temperature profile rather than a supersaturation profile simply because of ease of measurement.
- An alternative approach is to follow the supersaturation profile in the metastable zone using ATR UV-Vis measurements, i.e. closed loop control applies a feedback strategy to calculate the desired control effect.



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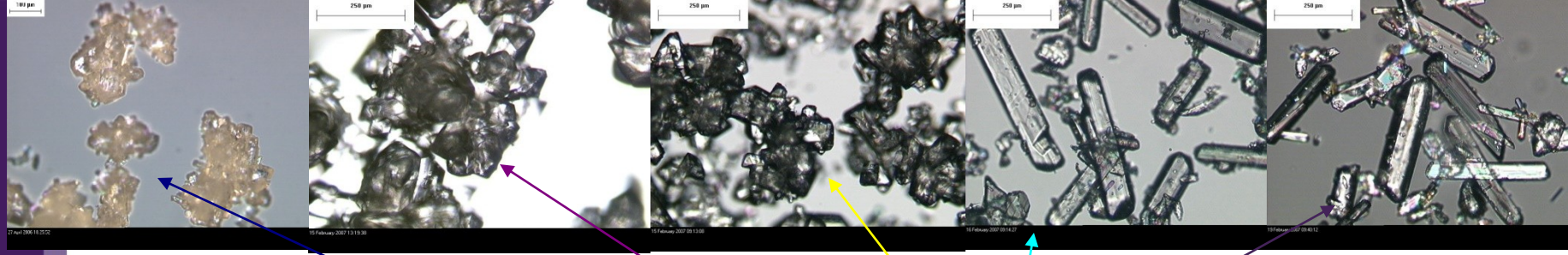

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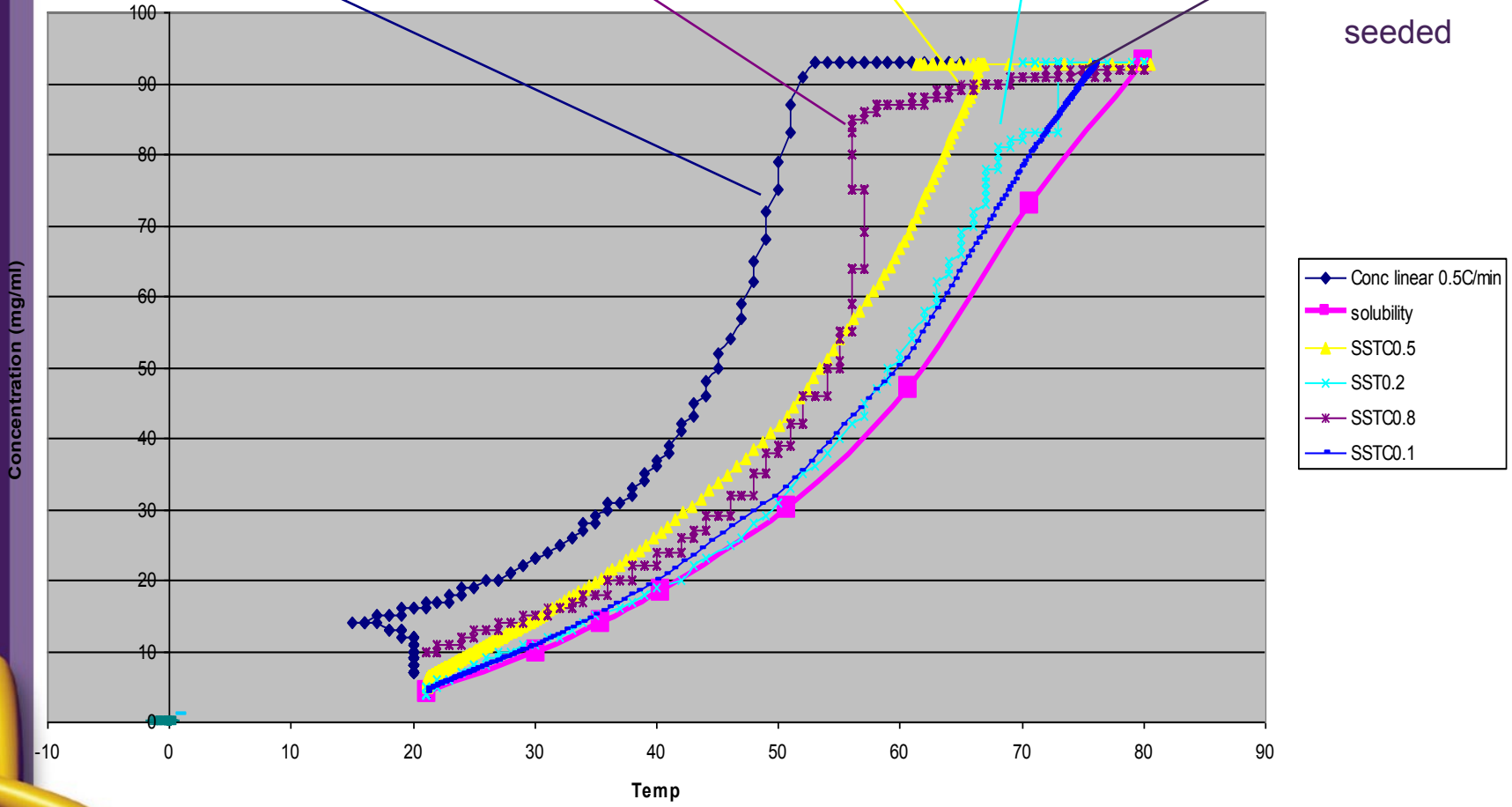

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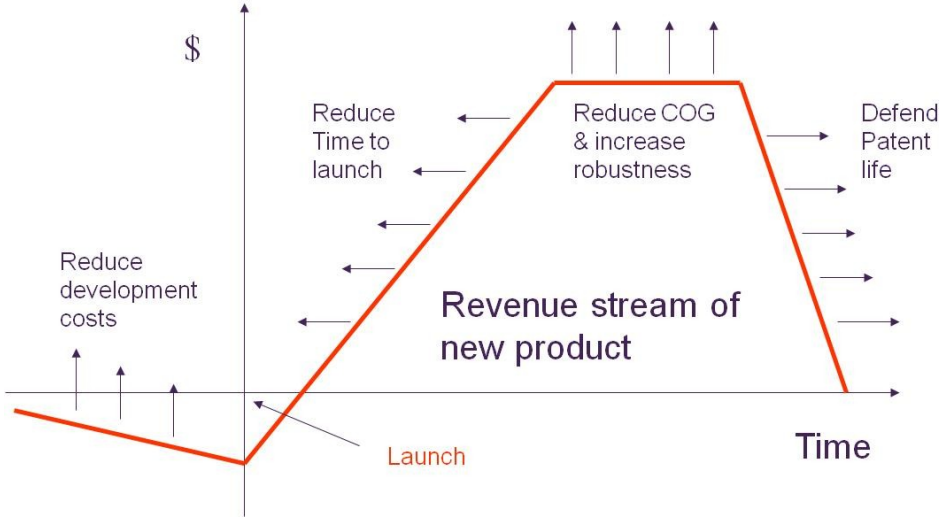
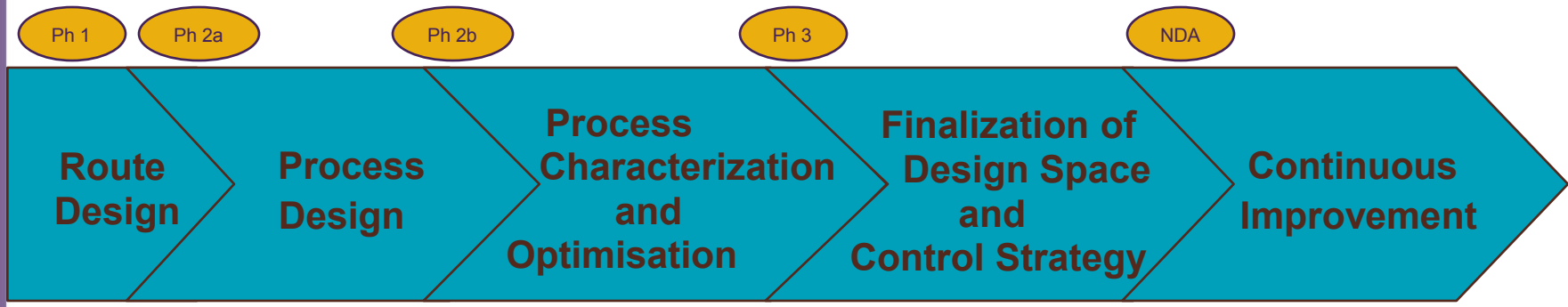
Justifying the cost benefit

- Increasingly difficult to justify new technology in R&D
- Consider Net Present Value



- More effective to build in Quality by Design using PAT as tool
  - Reduced development costs (focused development)
  - Speed up time to launch
  - Increase process robustness

PAT and QbD



- PAT is an enabling tool for QbD
  - Together with QRA's (to establish the drug substance CQA's) and experimental design to give focussed development
- PAT can help to gain process understanding during route design and process design phase
- Feed information into QRA's during Process characterisation / optimisation phase (iterative process)
  - Use the process understanding/knowledge to define the design space

Finalising the Design Space and Control Strategy

- Decide on the use of PAT in the registered Design Space
  - Understanding of process is good and process is robust – potentially drop PAT
- Potential to use PAT in control strategy
  - Is an IPC critical for the process/quality of product?
- Consider in-line PAT as alternative to off-line or at-line IPC's
  - Get smart and use closed loop feedback control
- In addition to delivering drug substance quality, in QbD consider commercial opportunities to use PAT/in-line analysis,
  - Realise potential processing efficiencies and RTR in commercial manufacture
  - Further opportunities for PAT
    - Monitoring process behaviour during TT and scale-up (troubleshooting)
    - Continuous process verification
    - Alternative to traditional Process validation - transferring process knowledge from lab scale to manufacturing plant

Summary

- Overview of how we're using in-line analysis (PAT) in AZ Process R&D
  - Real time data to increase process understanding (key driver) use this to improve our knowledge of design space
  - Typically use univariate and multivariate models, which scale up well
  - Evolved from monitoring processes to using feedback control
- Seen benefits of speed and quality using flexible PAT infrastructure from lab to plant
  - Cost effective compared to piece meal approach
  - Taken process understanding from lab to plant
- To realise full cost benefits, need to consider the big picture and use QbD to embed PAT in processes

Acknowledgements

- **PAT Team**
  - Nick Pedge, Richard Hart, Mandip Athwal
  - Andy Phillips, Mats Ridemark
- **PAT infrastructure**
  - Bill Moss, Martin Whitehouse, Dave Ennis
  - Mike Baker, Stephen King, Paul Byham, Steve Birket, Ben Nye
  - **Clairet Scientific** - John Andrews, Paul Dallin, Paul Kelly
- **AZ Projects**
  - Gerry Steele, Simon Watkins, Eric Merifield, Annabelle Germon, Lee Griffiths, Colin Benison, Gareth Howell, Rob Woodward, Steve Eyley, Marijan Stefinovic

Thanks for your attention

Any questions ?

Additional slides

Use of Raman ATEX rating

- Restricted use <35mW in gaseous flammable atmosphere
  - Can tune up to 400mW, typically use 300 –400mW
- Justified on basis of KOSI risk assessment
- Specific risk assessment
  - Probe tip immersed
    - BROV disabled when Raman connected
  - Reactor headspace inerted
    - Utilise cable interlock to deactivate laser
    - Vessel inert flag required before laser can be activated

GMP purposes

- Probes, spectrometers qualified GMP
  - Materials in contact, temperature and pressure
- Fibres commissioned, installation and testing fully documented
  - Tested attenuation, spectral integrity
- QA view
  - Equipment/users qualified then method OK for GMP if validated (early/mid development emphasis is on method verification)
  - Corporate guidelines for validating methods MVA
  - Treat same as any other technique for process monitoring
- PAT used for GMP in-process controls