Telescoped Reaction at Multiple Scales: Application of Mid-IR

Ian Clegg[1]

working with C.M. Gordon[2], M. Hanna-Brown[1], D.A. Harris[1], K. Meldrum[2], M.A. Velazco-Roa[1], S.P. Yeo[1] and May Ling Yeow[1]…and acknowledgements to several other colleagues

[1] Pfizer Global R & D, Analytical Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK
2 Pfizer Global R & D, Chemical R&D, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

A summary of this presentation:

- **A project based example of using PAT during process development and scale up:**
  - The process is a telescoped API reaction and Mid-IR has been applied to all three sub-stages.
  - Mid-IR has been used throughout the development lifecycle
  - Consistent Mid-IR data has been obtained from ~50cm3 scale to >1000 Litres
  - The spectral details include multiple useful features

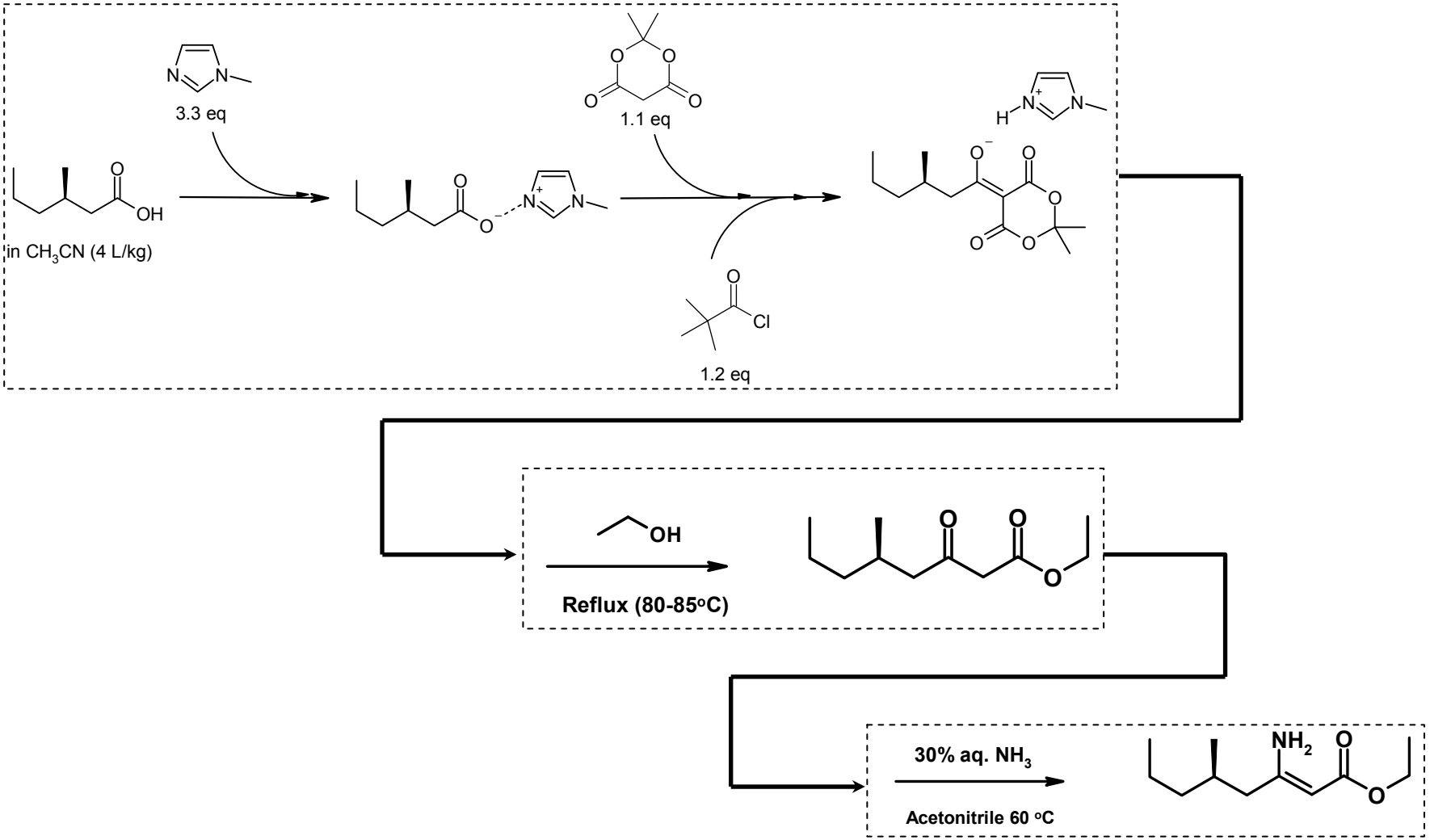
Why investigate Mid-IR for this stage?

- **The reaction is telescoped and the overall reaction times is long (up to 80 hours in the pilot plant).**
  - In-Situ monitoring would enable the cycle time to be reduced: an important benefit for manufacturing.
- **Some of the reaction intermediates are unstable and difficult to assay.**
  - We avoid lengthy development of an off-line technique: even when developed, the method that could be difficult & expensive to deploy
- **No chromophores → difficult analytics but potentially PAT-friendly**
- **The specifications for the reaction end point are relatively wide (several percent starting materials): the limited sensitivity of vibrational spectroscopy unlikely to be an issue.**
- **There are HSE concerns with some of the reactants (e.g. the acid chloride) and concerns over the need to sample at reflux.**

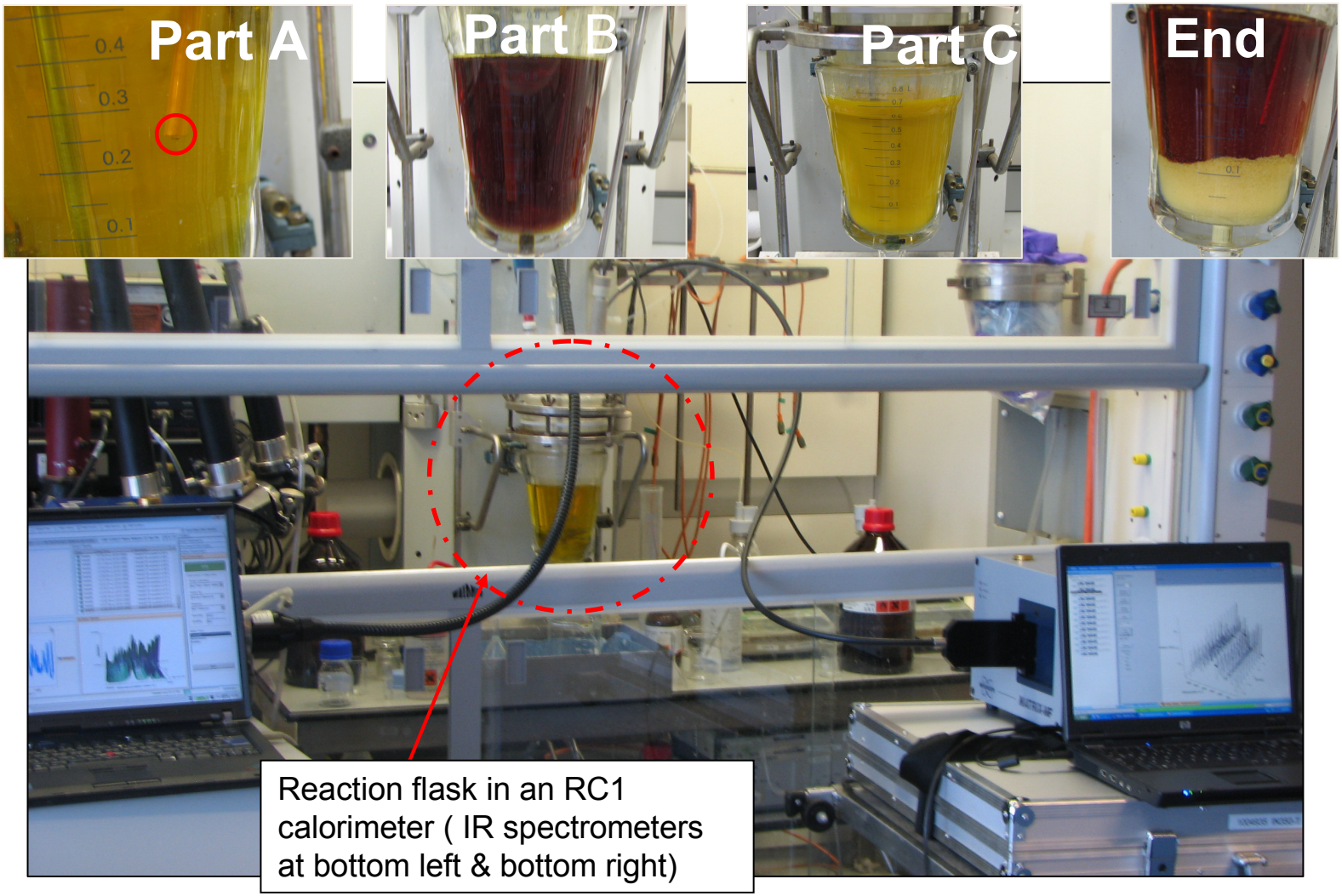
Some more detailed objectives

- **Increase the degree of process understanding by developing the design space for this reaction.**
  - Simple design using reagent stoichiometries as the variable
  - Min/max limits set by considering possible operational tolerances at scale.
  - Determine the sensitivity of Mid-IR to build a quantitative model in a retrospective way
- **Evaluate the effect of a "worst case scenario" of ingress of water in the system to determine response.**

The telescoped stage:



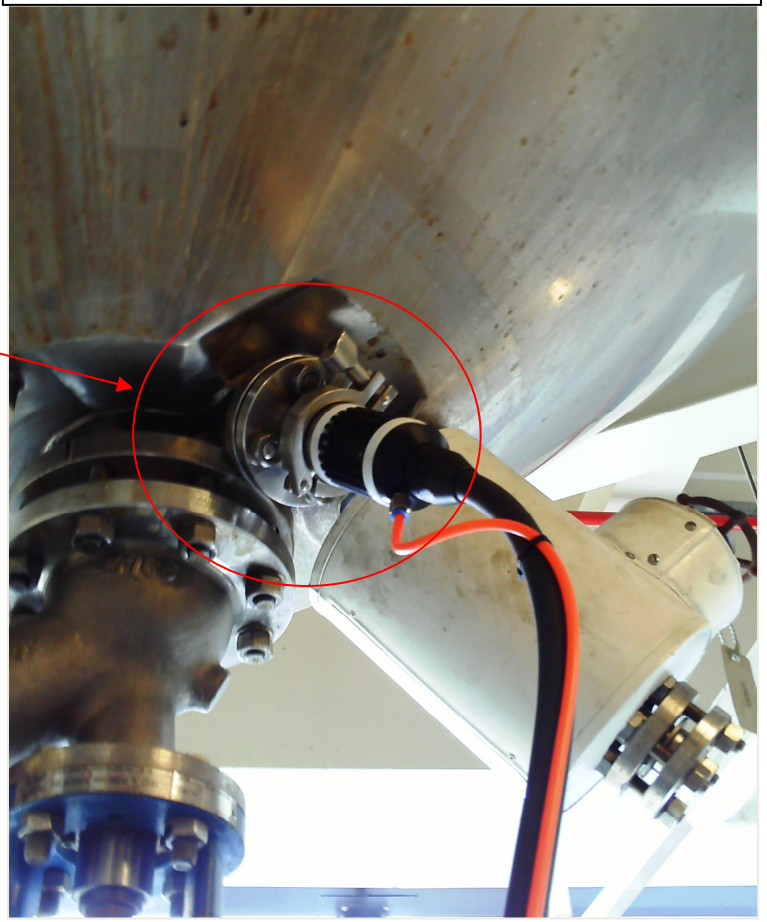
Typical lab based measurement configuration



Typical Spectrometer layout in the pilot plant

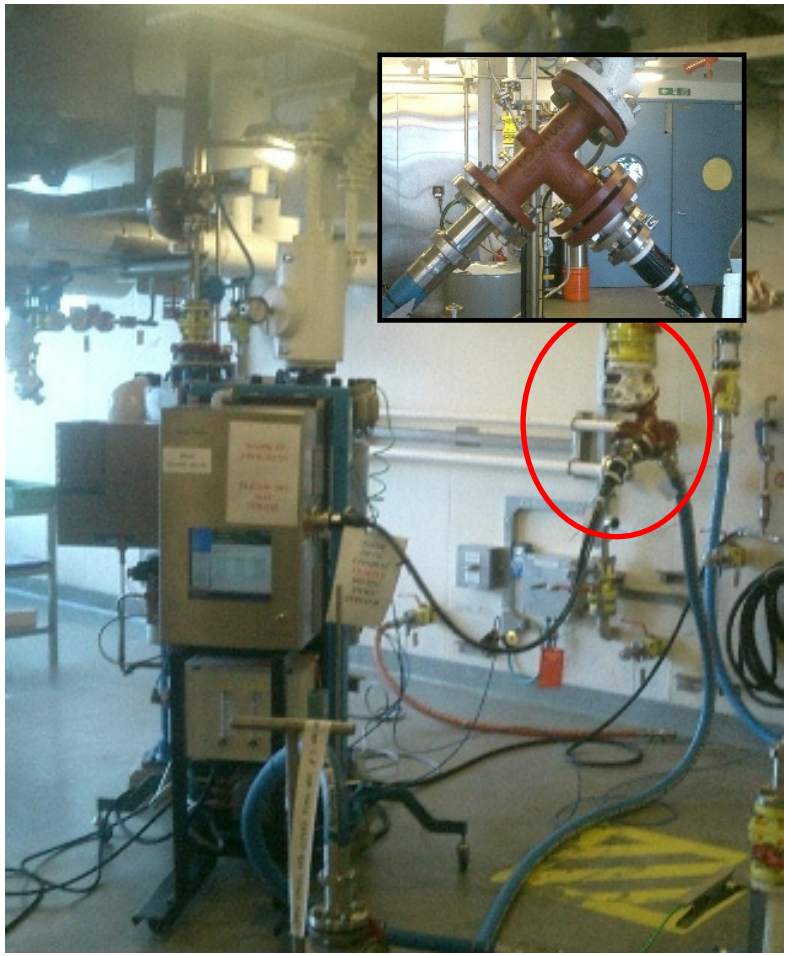
General Layout: spectrometer to foreground

The location of the measurement probe in the vessel

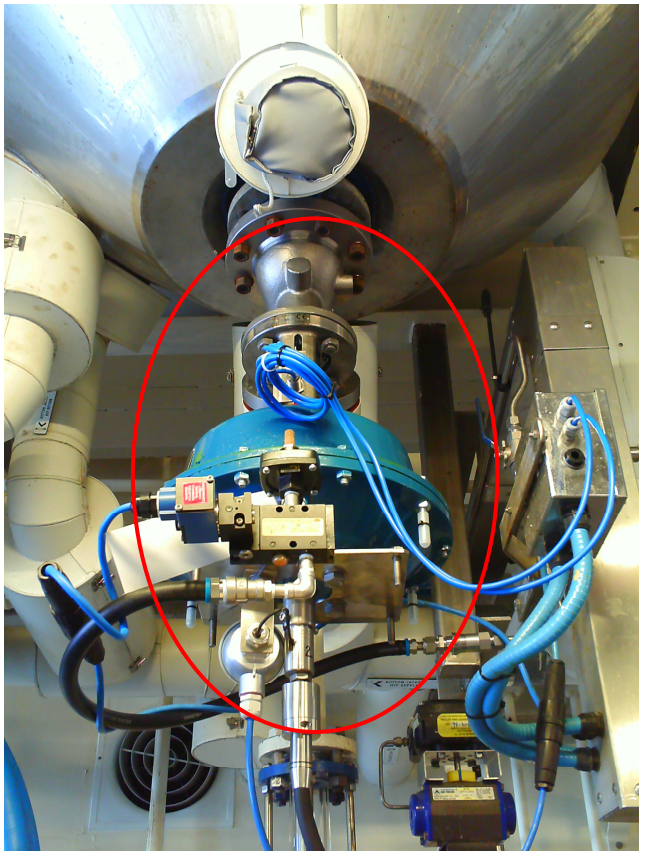


Other possible configurations at scale

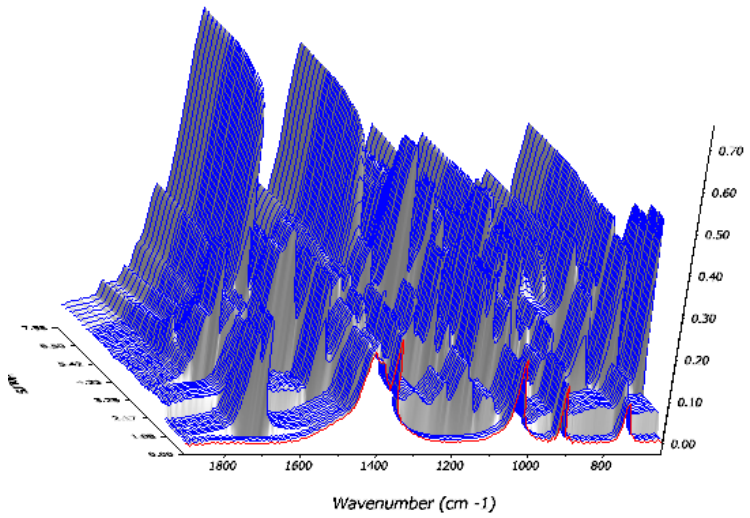
Pump Around Circuits



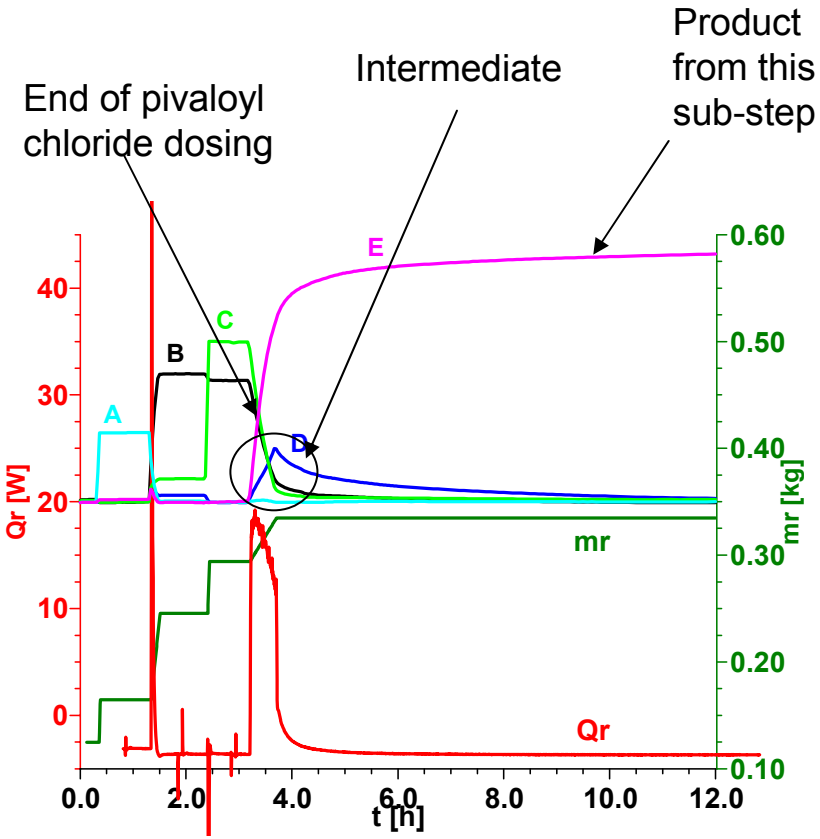
Foot Valve



PAT experiments / assessments started very early on in the development….

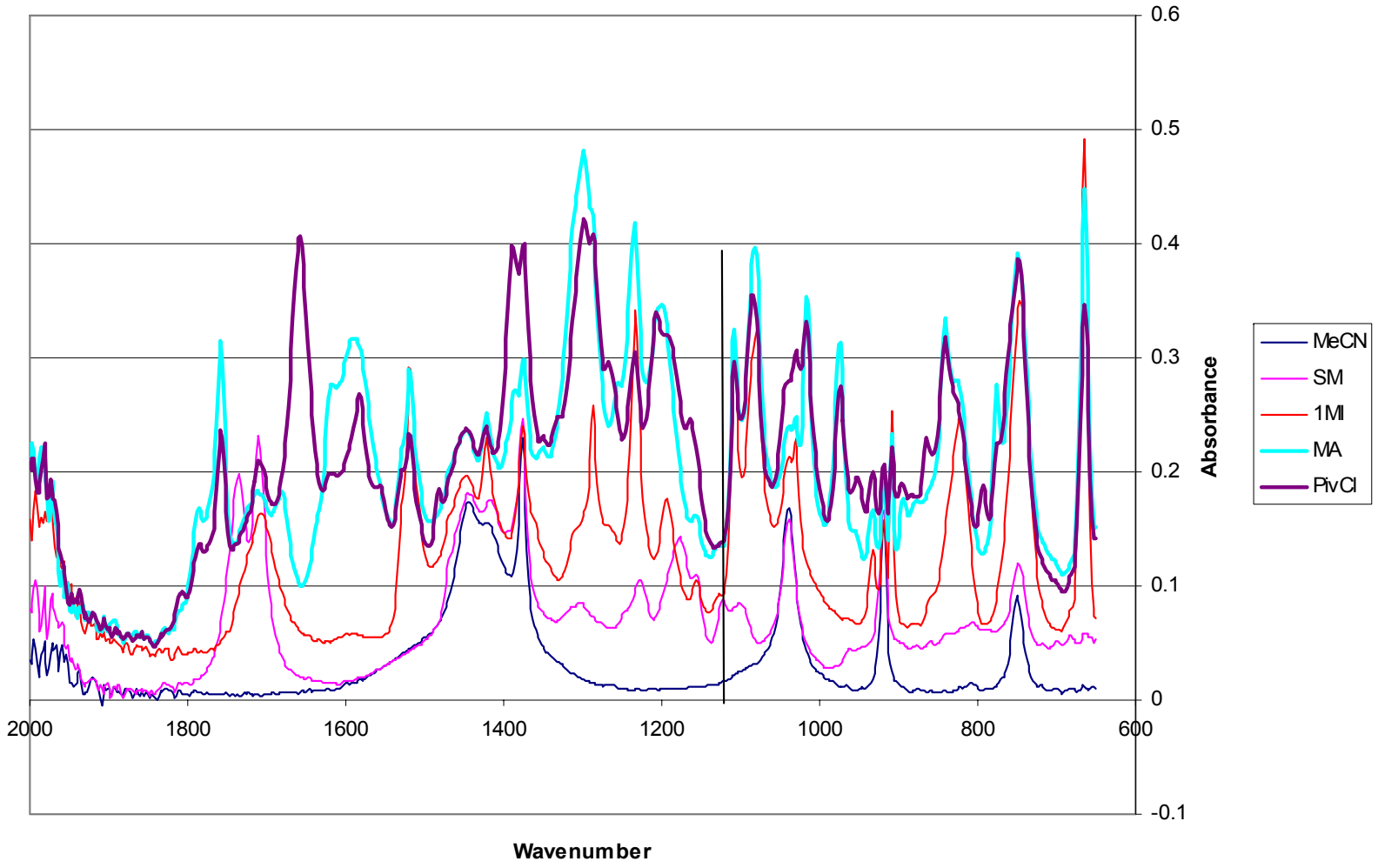


Initial waterfall plot obtained in a lab scale reactor (50 cm3) for all three sub-stages



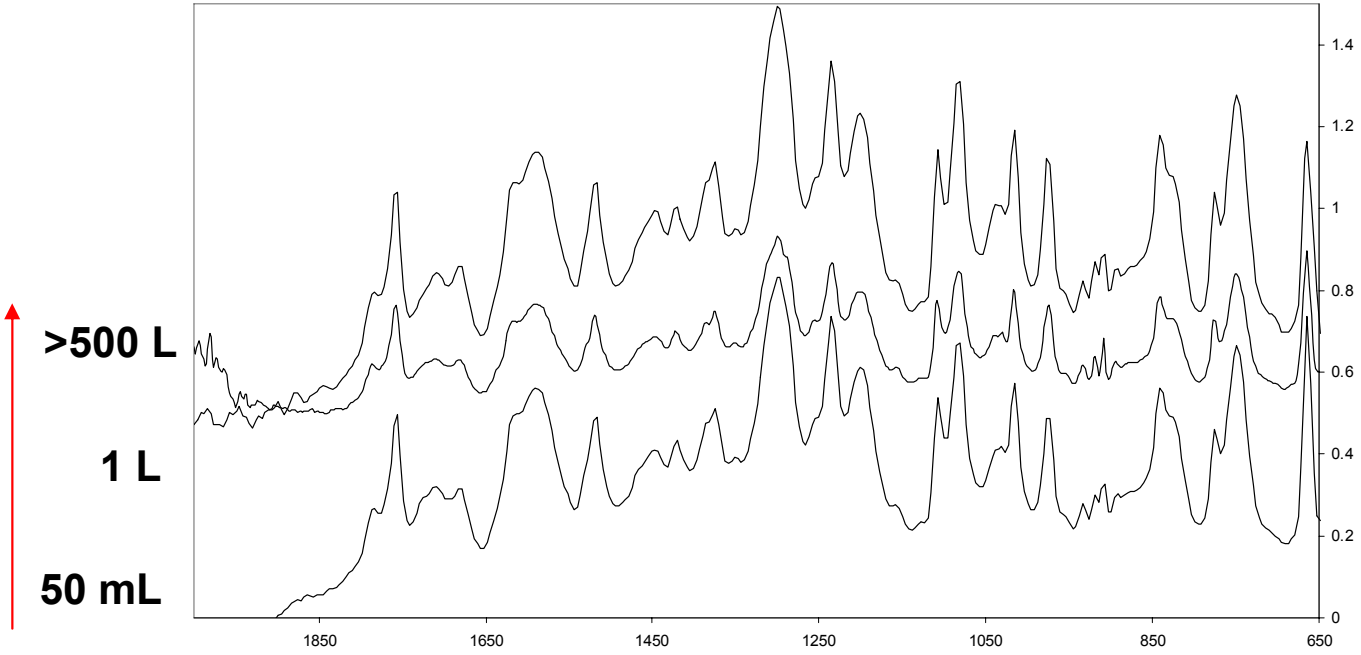
Processed IR and RC1 data
Reaction ~85% complete at end of dosing, but required ~6 hours to reach completion

Spectrum overlays (Part A)

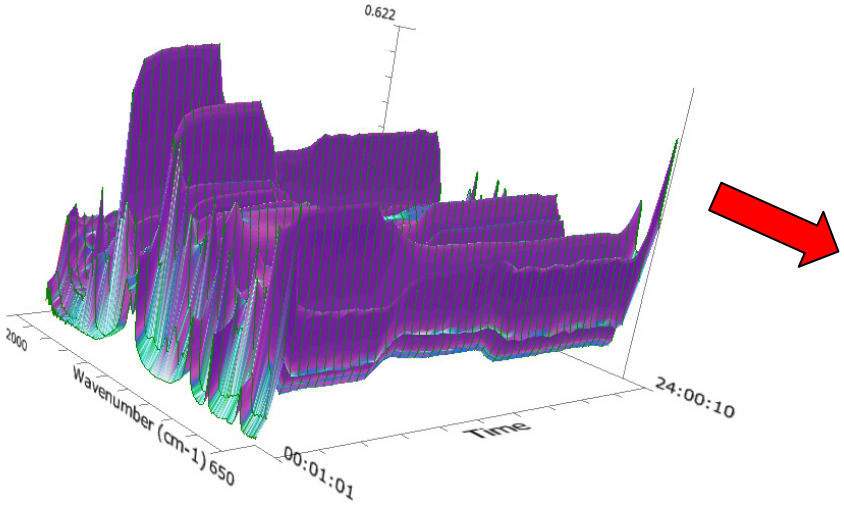


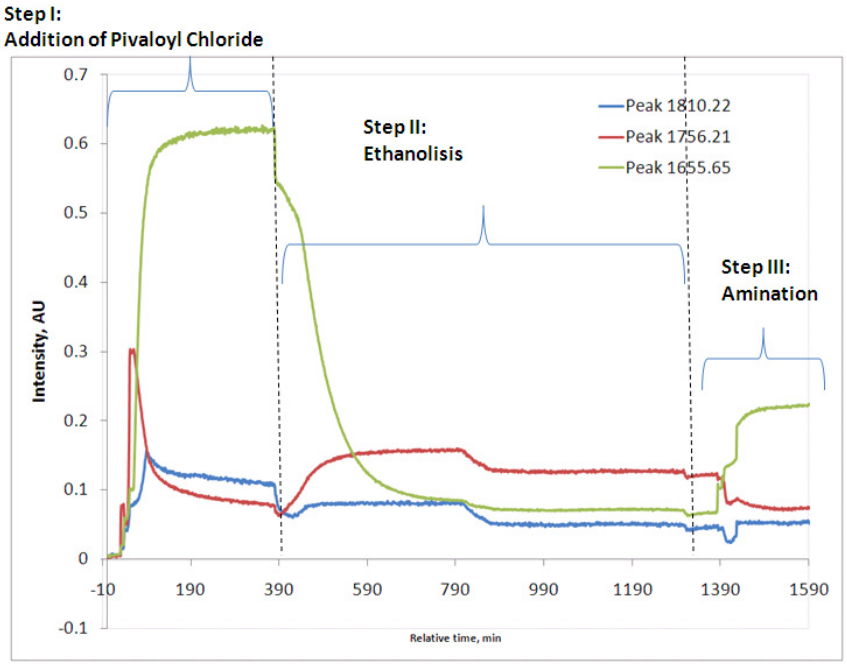
Step A: excellent potential for PAT application

- **All main species display distinctive IR features**
- **DoE-type approach used to develop a quantitative model**
  - Offline analysis allowed effective calibration of FTIR data
- **FTIR data recorded for four pilot plant batches**
  - Excellent corroboration between scales (see below)
  - Clear changes during reaction (next slide)



Mid-IR data obtained from the whole reaction



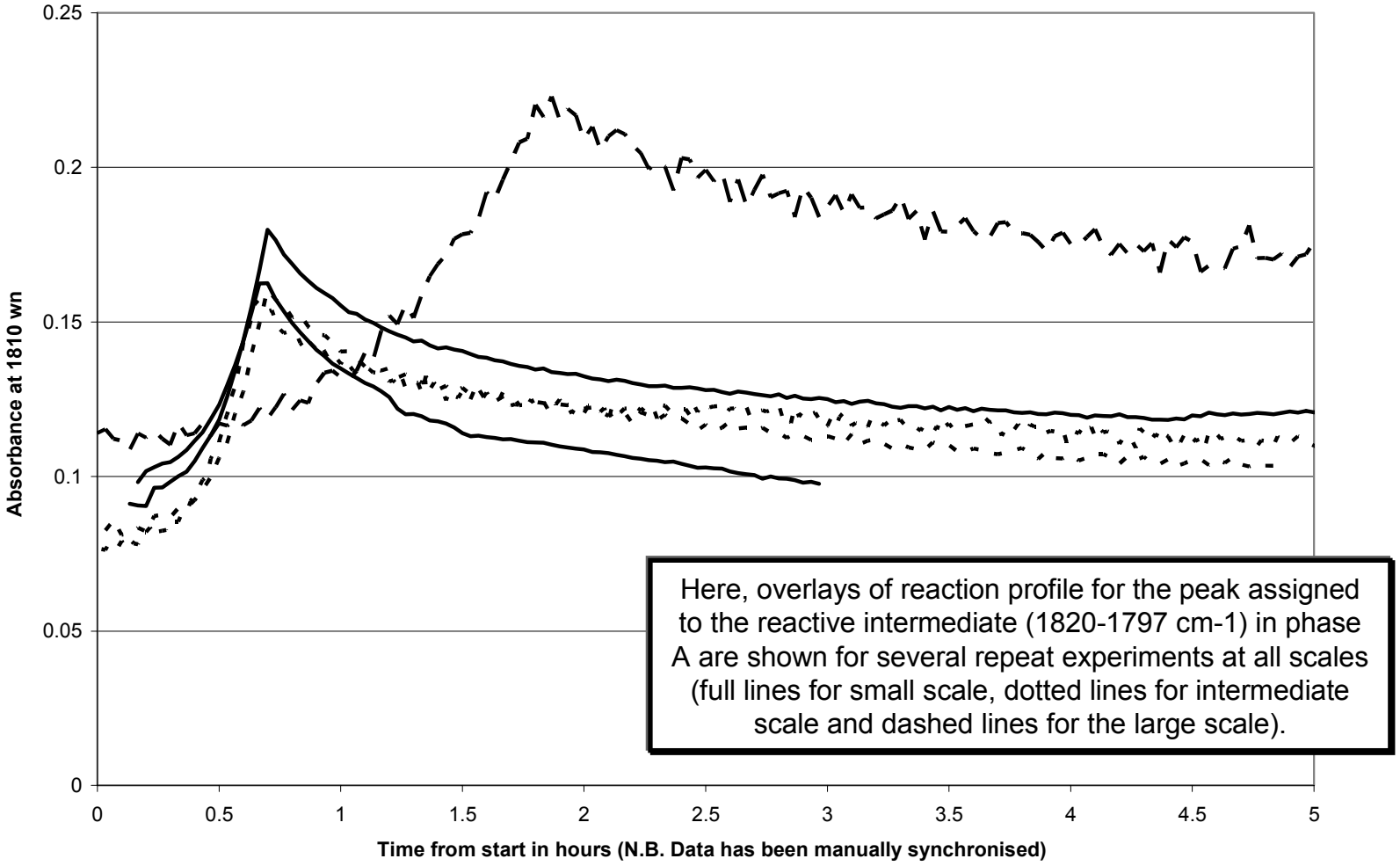


Identified peaks:

- **1756 cm^{-1} SM and Meldrum's acid**
- **1810 cm-1 Pivaloyl anhydride**
- **1655 cm^{-1} Product**

See Also - http://www.youtube.com/watch?v=EWec0O6WtUU

The data on the reactive intermediate was key:



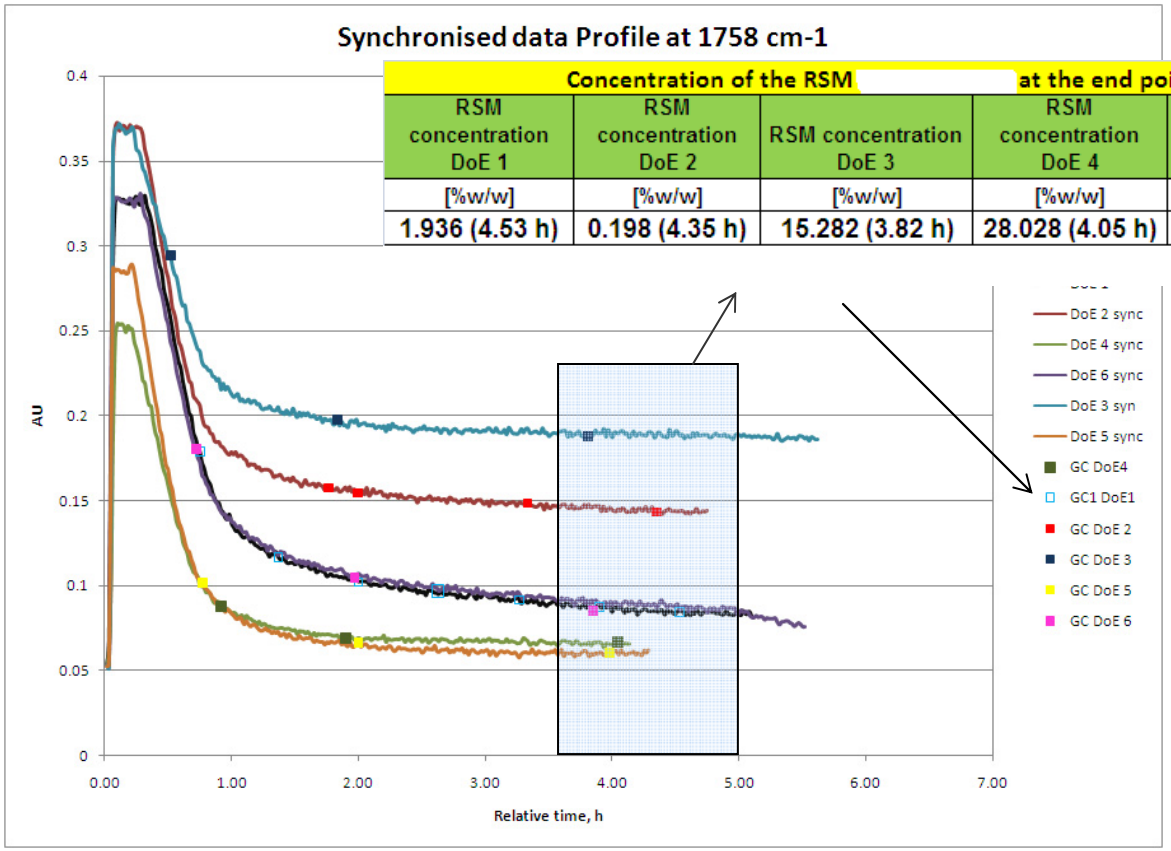
Here, overlays of reaction profile for the peak assigned to the reactive intermediate (1820-1797 cm-1) in phase A are shown for several repeat experiments at all scales (full lines for small scale, dotted lines for intermediate scale and dashed lines for the large scale).

DoE evaluation: An initial evaluation of design space (for the first part only)

- A design to evaluate the effect of two factors: amount of pivaloyl chloride and meldrum's acid.
- To build the data set 7 samples were collected during DoE 1 at standard conditions after the addition of pivaloyl chloride. 3 IPC samples were taken at the same intervals for each during the remaining runs of the DoE (6 reactions in total). 1-MIM was fixed at 3.3 eq.
- The IPC samples taken during the DoE were analysed using GC to determine RSM. The calibration data set generated during Run 1 was used to build a calibration model using chemometrics (PLS, PCA).

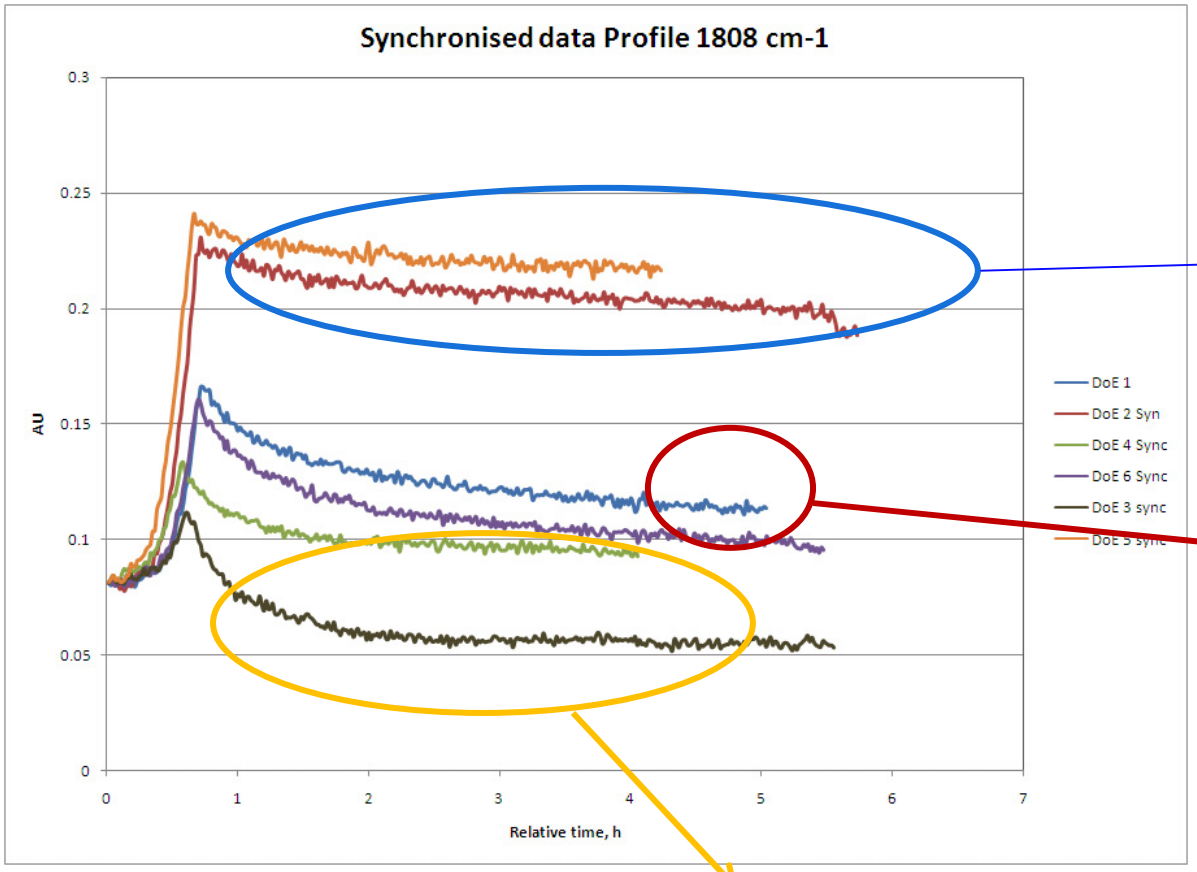
Run Order	Pivalyol chloride	Meldrum's acid
1	M	M
2	H	H
3	L	H
4	L	L
5	H	L
6	M	M
Low Setting	0.9 eq	0.9 eq
Mid Setting	1.2 eq	1.1 eq
High Setting	1.5 eq	1.3 eq

DoE: Synchronised profiles for product



Concentration of the RSM at the end point of the reaction					
RSM concentration DoE 1	RSM concentration DoE 2	RSM concentration DoE 3	RSM concentration DoE 4	RSM concentration DoE 5	RSM concentration DoE 6
[%w/w]	[%w/w]	[%w/w]	[%w/w]	[%w/w]	[%w/w]
1.936 (4.53 h)	0.198 (4.35 h)	15.282 (3.82 h)	28.028 (4.05 h)	8.7 (3.98 h)	4.154 (3.85 h)

DoE: Peak associated to pivaloyl anhydride (intermediate product)

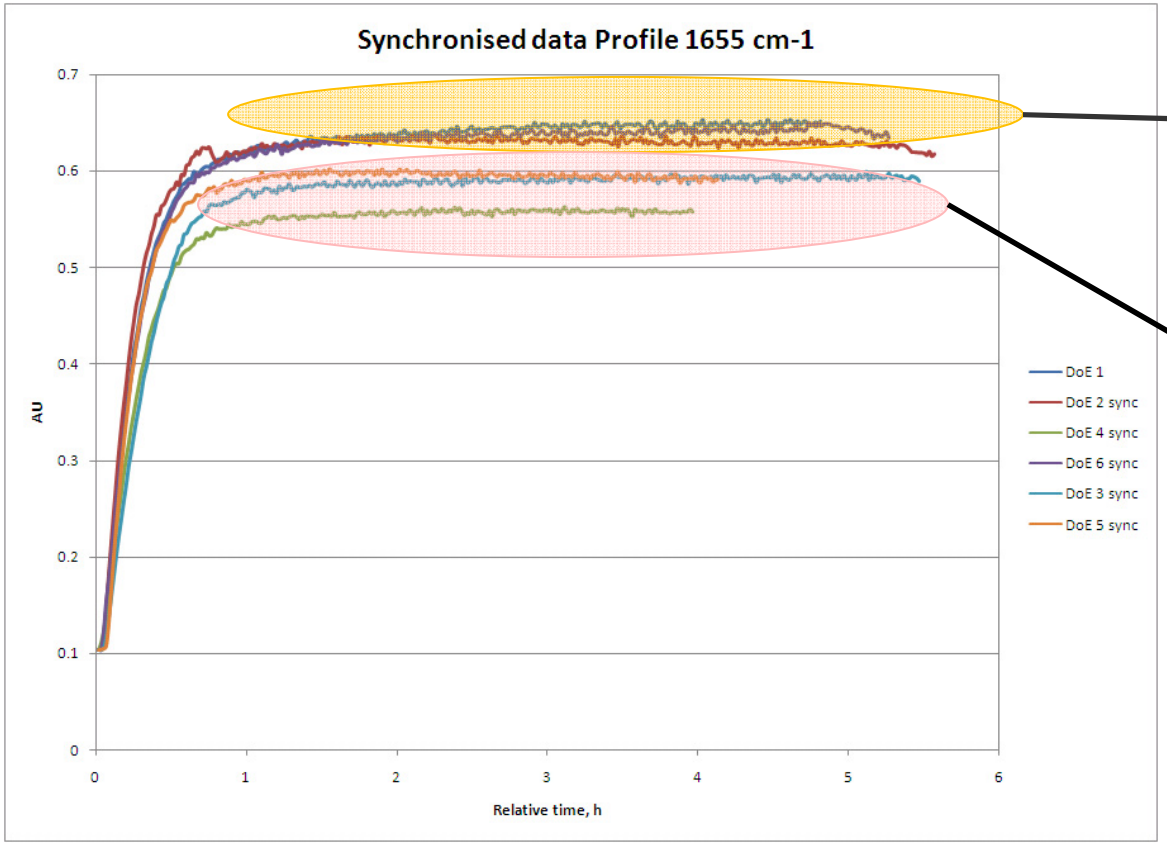


DoE 2 and DoE 5 Piv chloride was added in excess, more piv anhydride is produced and tends to disappear slowly

DoE 1 and DoE 6 Pivaloyl Chloride was added at the standard conditions for the reaction .?

DoE 3 and DoE 4 - reduced amount of Piv chloride was added

DoE: Tracking the product

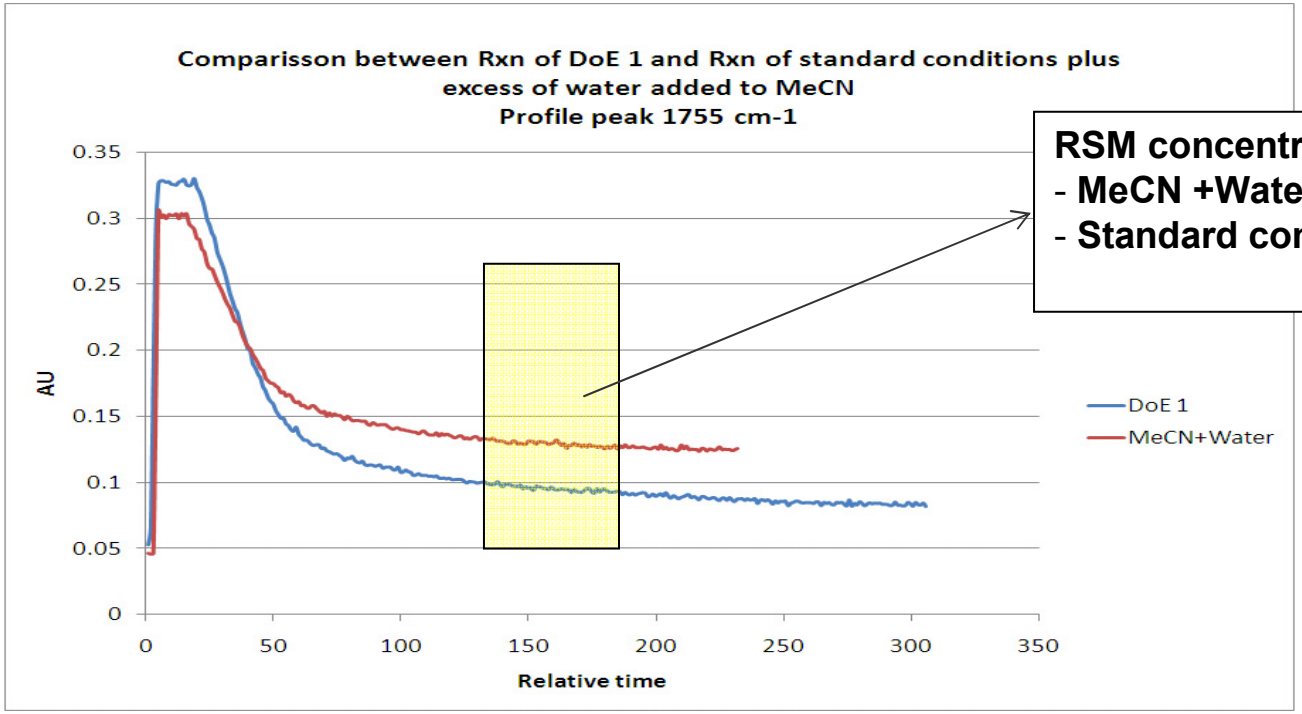


Indicates that the excess of SM does not increase the conversion of the SM to product

Indicates that there is a shortage of one of the SM then the target conversion to PF-04579767 is not achieved.

Standalone experiment: Simulation of "worse case" scenario of input of water in the reaction system

- **Acetonitrile + water: reaction was run @ standard conditions: 1.5% w/w of water was added to MeCN.**



RSM concentration at the end point:
- **MeCN +Water: 21.1% w/w**
- **Standard conditions: 1.934 % w/w**

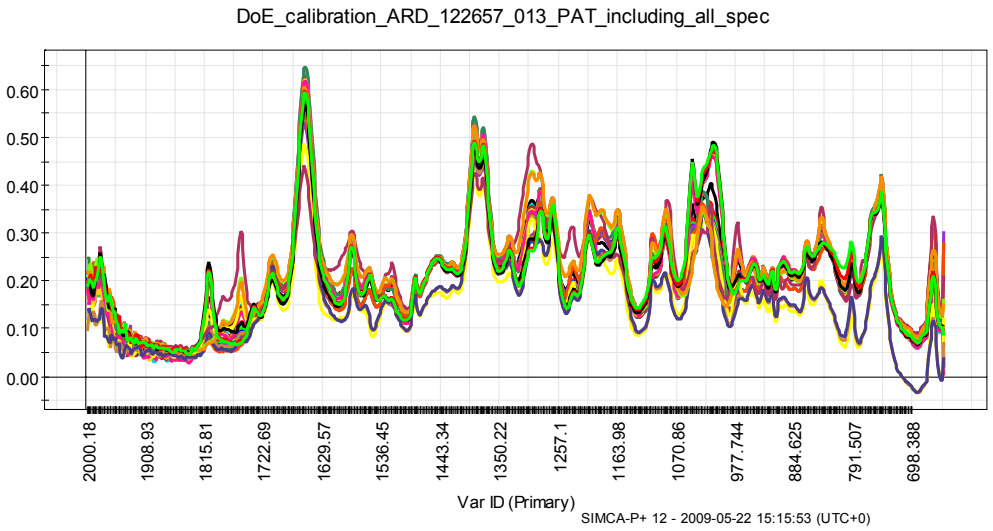
Model Development overview

- SM and products didn't have distinctive peaks so a univariate model was not possible.
- Multivariate calibration model was the best approach in this particular case as the spectral data was very complex. In this case a PLS regression model was used to build the quantitative calibration model.
- Several model iterations were required in order to tune (by removing outliers, changing the wavelength range etc.) – the best model is shown here….

Calibration model using PLS: Partial Least Squares

Training set for the calibration:

Spectral data from the DoE evaluation

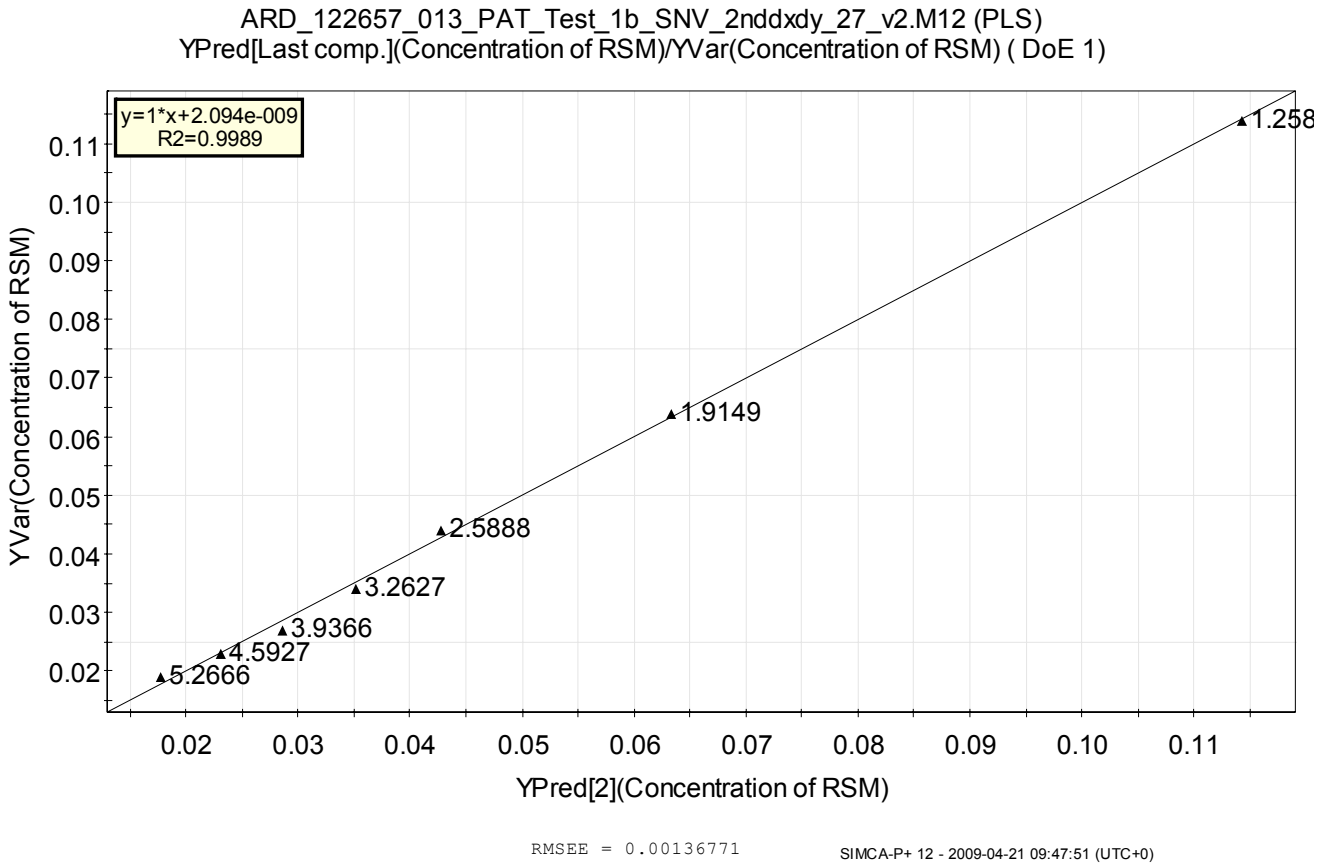


Off-line GC data

Time [h]	DoE	Concentration
1.2588	DoE 1	DoE 1 (RSM 11.4 %)
1.9149	DoE 1	DoE 1 (RSM 6.4%)
2.5888	DoE 1	DoE 1 (RSM 4.4%)
3.2627	DoE 1	DoE 1 (RSM 3.4%)
3.9366	DoE 1	DoE 1 (RSM 2.7%)
4.5927	DoE 1	DoE 1 (RSM 2.3%)
5.2666	DoE 1	DoE 1 (RSM 1.9%)
2.5324	DoE 2	DoE 2 (RSM 2.05%)
2.7805	DoE 2	DoE 2 (RSM 1.8%)
4.1978	DoE 2	DoE 2 (RSM 0.4%
5.2785	DoE 2	DoE 2 (RSM 0.2%)
2.5861	DoE 4	DoE 4 (RSM 30.4%)
3.9148	DoE 4	DoE 4 (RSM 28.2%)
5.9168	DoE 4	DoE 4 (RSM 28%)
1.3787	DoE 6	DoE 6 (RSM 12.4%)
2.7046	DoE 6	DoE 6 (RSM 7.3%)
4.7028	DoE 6	DoE 6 (RSM 4.2%)
1.8703	DoE 3	DoE 3 (RSM 21.1%)
3.2015	DoE 3	DoE 3 (RSM 16.2)
5.2066	DoE 3	DoE 3 (RSM 15.3%)
1.2325	DoE 5	DoE 5 (RSM 10.7%)
2.4819	DoE 5	DoE 5 (RSM 9.4%)
4.491	DoE 5	DoE 5 (RSM 8.7%)

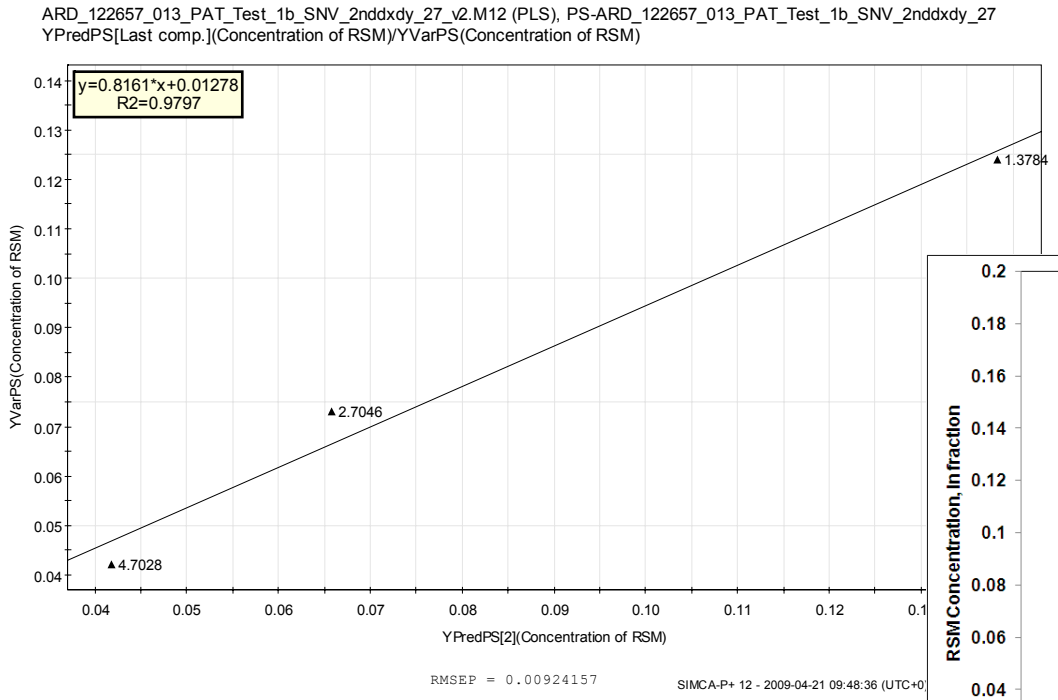
DoE 6 (which was a repeat of DoE1) was left as the test set

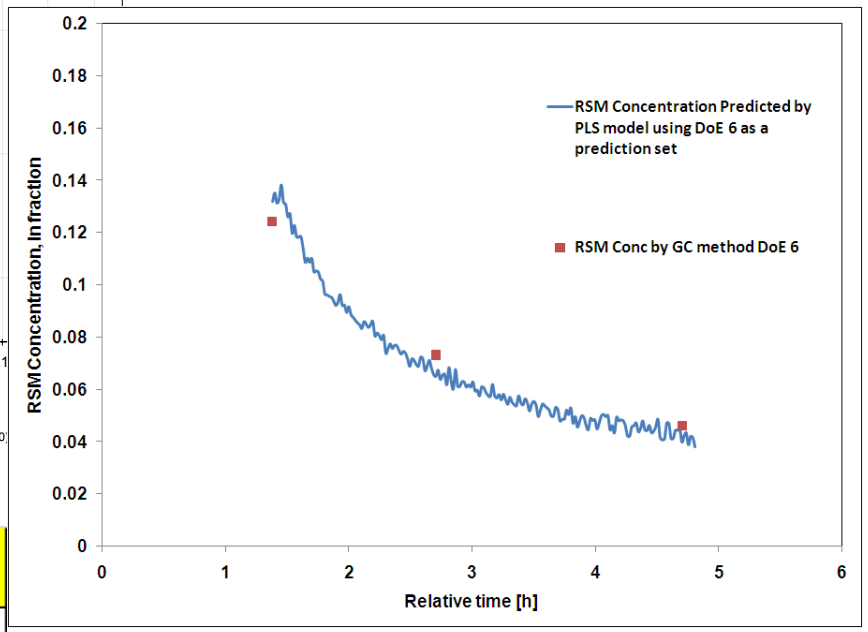
PLS calibration model 2



- Training set: DoE 1 standard conditions
- Wavenumber region: 1776.7 cm-1 – 1650 cm-1
- 2 factors
- R2Y(cum)= 0.999 Q2(cum) = 0.996

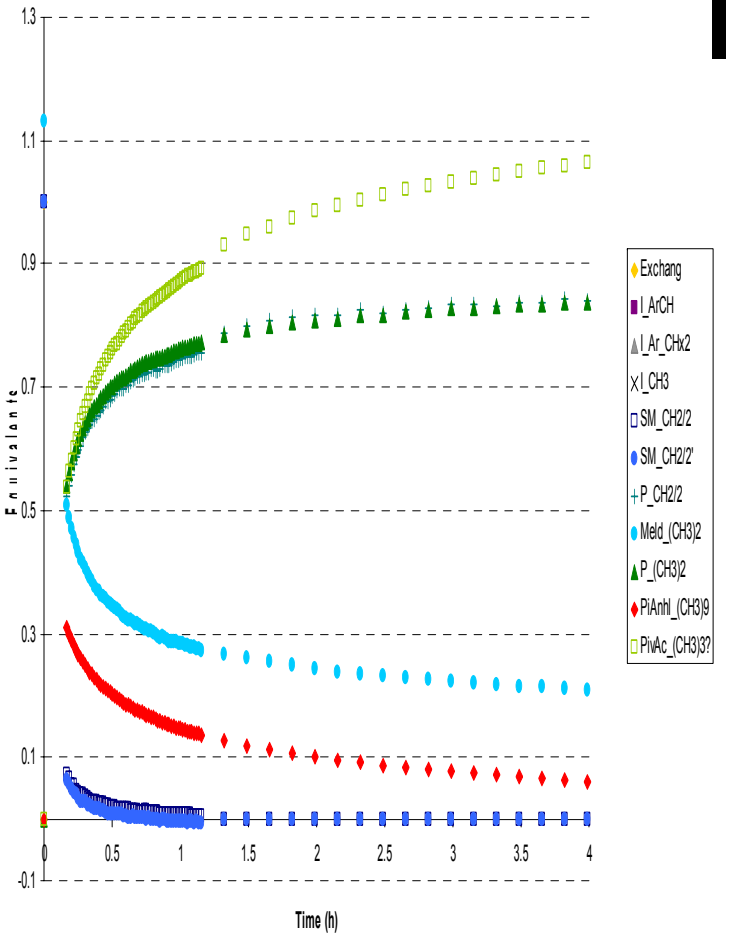
Model 2 potential for prediction



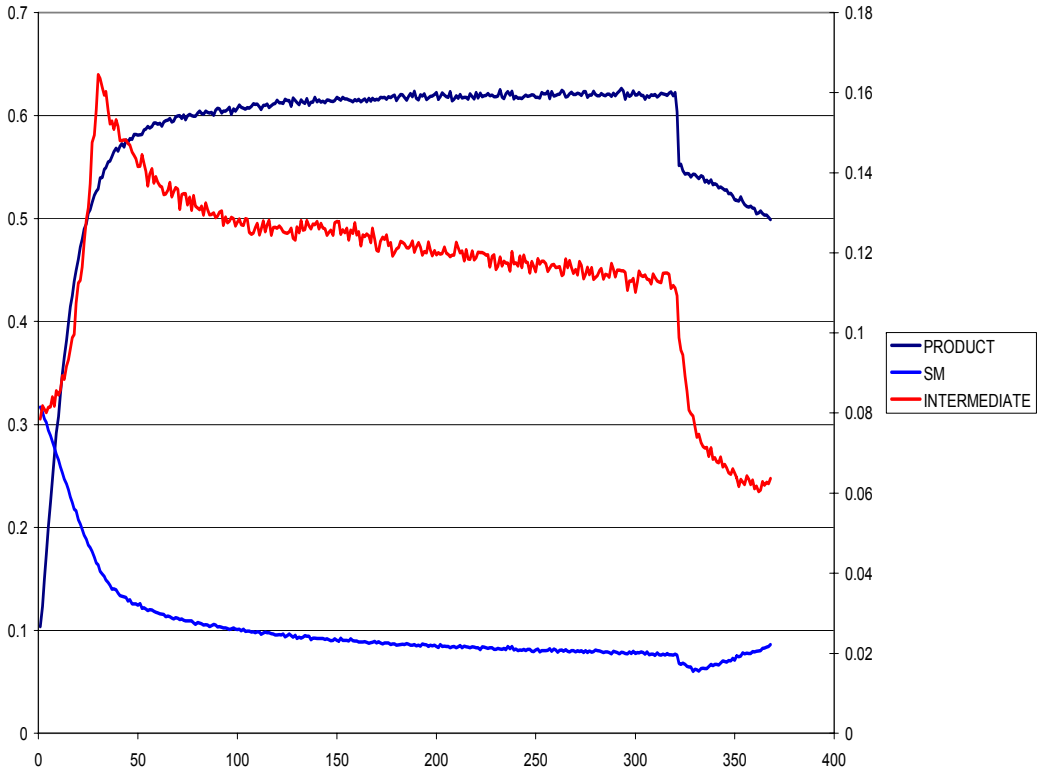


RelativeTime [h]	RSM Conc by GC [%]	Conc Predicted by PLS [%]	Absolute Error [%]
1.3787	12.4	13.2	0.79
2.7046	7.3	6.6	0.72
4.7028	4.6	4.2	0.42

NMR


1.3
1.1
0.9
0.7
0.5
0.3
0.1
-0.1
0
0.5
1
1.5
2
2.5
3
3.5
4
Time (h)
Exchang
I_ArCH
I_Ar_CHx2
I_CH3
SM_CH2/2
SM_CH2/2'
P_CH2/2
MeId_(CH3)2
P_(CH3)2
PiAnhl_(CH3)9
PivAc_(CH3)3?

IR


0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
0
50
100
150
200
250
300
350
400
PRODUCT
SM
INTERMEDIATE

Conclusions and closing remarks pt #1

- **Complementary**
  - The two approaches disclosed have complementary strengths and different limitations.
- **Standardisation**
  - All the equipment described here is standard and “off the shelf”.
- **Scaling**
  - The data is consistent across multiple scales from <1cm3 to ca. 1000L and between different instruments and methods.
- **Collaboration.**
  - Development of a PAT approach requires close collaboration between chemists and analysts in the development teams.
- **Timing**
  - The start of development of PAT methods should be early

Conclusions and closing remarks pt #2

- **DoE**
  - An early provided critical information about the design space / robustness of the chemistry and the calibration of the Mid-IR
- **Cycle Time Reduction**
  - The potential for using Mid-IR to reduce cycle time by ca. 25% is a powerful driver for implementation.
- **Control**
  - The use of PAT may also allow us to use different manufacturing control methods

Reference Materials

- **Some data has been uploaded to Youtube:**
  - Mid-IR data (Feb 2010): http://www.youtube.com/watch?v=EWec0O6WtUU
  - NMR data (June 2010): http://www.youtube.com/watch?v=bpwbU2UntB4

- **See also papers that appeared in the Journal "The Chemical engineer", June and September, 2010**

Thanks for you kind attention

Questions ?