# Going with the Flow –
## *the evolution from batch to continuous hydrogenation*

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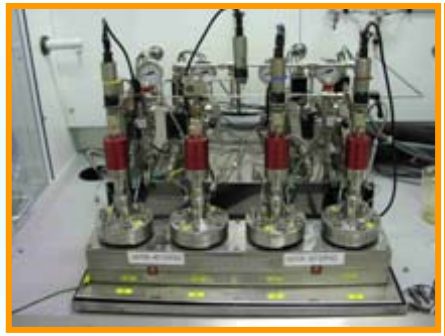
# Outline

- Prior GSK hydrogenation experience
  - Batch
  - Continuous
- The IMPULSE project collaboration
  - Background
- Continuous hydrogenation design
  - Applied to sumatriptan chemistry
  - CNRS-Lyon : aq. EtOH solvent process.
  - GSK : NMP solvent process.
- Conclusions
- Acknowledgments

# Prior GSK Experience - Batch



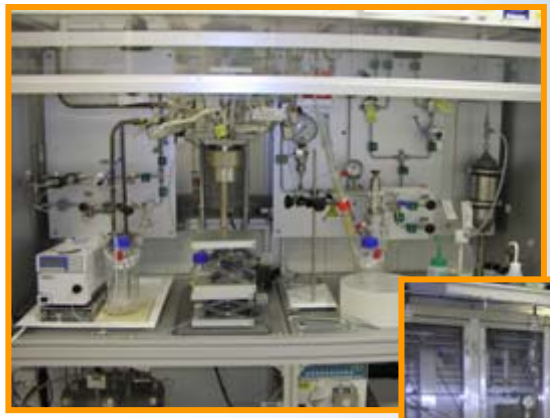
- Extensive design capability
  - Parallel screening/development, 2- 40ml scale.
  - Process verification, 0.5 – 20 litre scale.
  - Scale-up to plant, 200 – 1600 litres.
- Sound scale-up principles applied
  - Gas mass transfer ($k_La$) is fundamental scale-up parameter.
  - Self-aspirating agitators and high performance hydrofoils are employed to enhance reactor performance.

# Prior GSK Experience - Continuous

- MkI continuous hydrogenator
  - Custom design, installed in 2000
  - CSTR design, 50 - 500ml.
  - Proof of concept 2000-2002.
- MkII continuous hydrogenator
  - Custom design, installed 2003.
  - 2x 800ml CSTR, 1 x PFR in series or parallel.
  - Commissioned with model chemistry 2006.
- MkII Upgrade
  - GSK designed and installed 2 x PFR reactors 2008.
  - Duty / Stand-by mode to support the IMPULSE project.

# GSK Lab Continuous Capability

- GSK Tonbridge
  - CSTR
    - 40ml custom CSTR, 100 bar rated.
    - 2 x 800ml custom CSTR, 100 bar rated, in series or parallel operation.



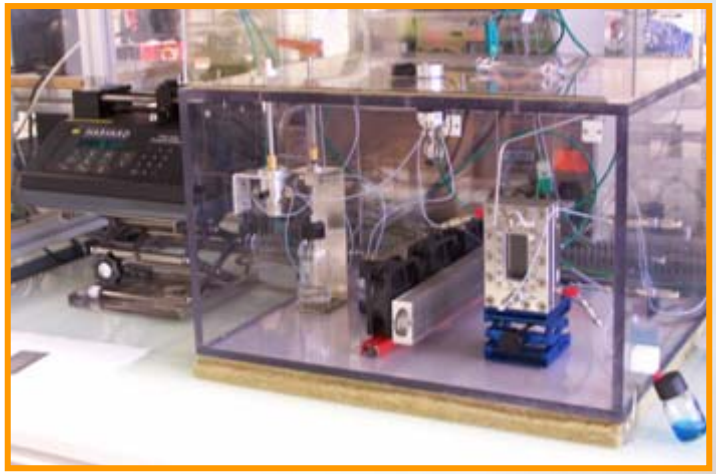
  - PFR
    - Custom 2 x 120ml PFRs, 100 bar rated.
    - Configured for duty/stand-by operation.
    - Designed and installed in 2008.

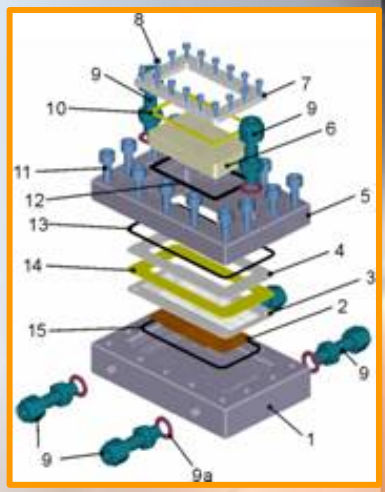
# IMPULSE – Continuous Hydrogenation

- **IMPULSE:**
  - **Integrated Multiscale Process Units with Integrated Structured Elements.**
  - **Goal: Replacement of batch processes by steady-state continuous flow systems.**
  - **Performance Objectives: Reduce costs and environmental impact, enhance product quality, process robustness and sustainability.**

- **Continuous Hydrogenation Demonstration**
  - **CNRS Lyon**
    - **Assess novel reactor types presented by Consortium Partners.**
    - **Conduct primary continuous hydrogenation evaluation with the model sumatriptan process.**
  - **GlaxoSmithKline**
    - **Provide infrastructure to install the selected reactor type.**
    - **Support demonstration experiments.**

# IMPULSE Reactor Design Decision

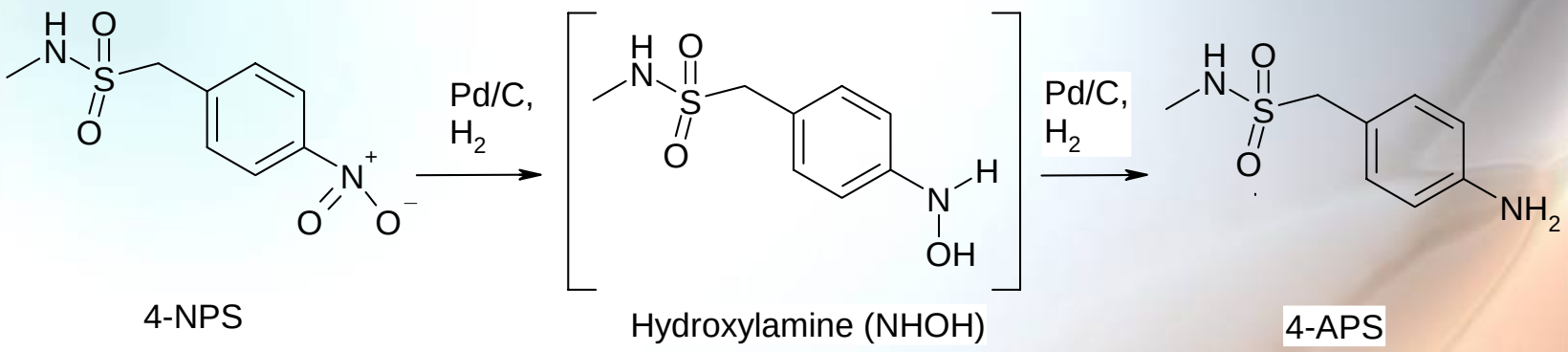





- A range of novel reactor designs supplied by IMPULSE consortium partners were assessed at CNRS Lyon.
  - Micro-structured falling film and packed bed reactors, mesh-stabilised film contactor.
  - None of the novel reactors were suitable for scale-up to the demonstration study.
  - Parallel studies on the test chemistries were conducted in “traditional” CSTR and PFR reactors.

- In January 2008 the decision was taken to progress with a PFR design for the demonstration in 2008-2009.
  - Consortium partners were approached to deliver a suitable demonstration PFR, however no reactor was delivered.
  - In parallel, GSK designed and installed a duty/stand-by PFR system as a contingency – this was employed for the demonstration.

# Sumatriptan process



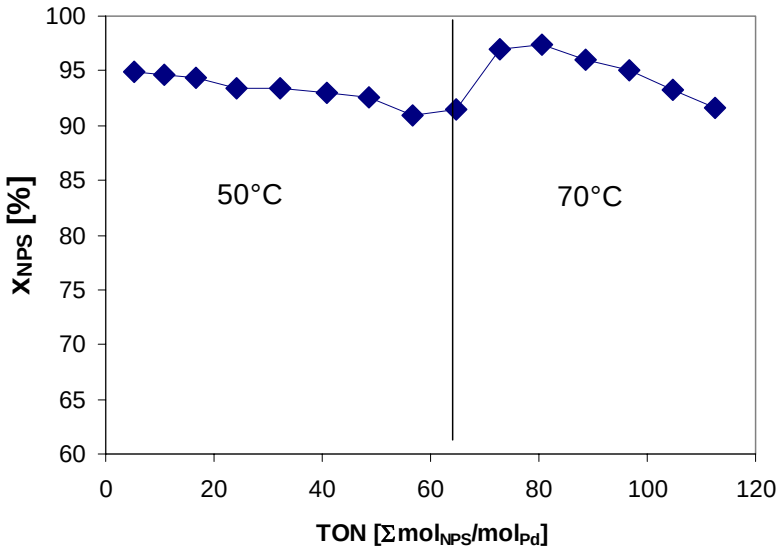

4-NPS

Hydroxylamine (NHOH)

4-APS

- The major reaction pathway is via the hydroxylamine (NHOH) intermediate.
  - Minor reaction pathway via azoxy dimer species.
- Commercial batch mode info
  - Initially a slurry (low solubility of 4-NPS in aq. EtOH).
  - 5% Pd/C powder employed, 5% w/w wrt 4-NPS.
  - Conducted at 70-80$^{o}$C, 1.4 bar, ~6 hrs (105kg input, 0.69M).
  - 4-APS soluble in aq. EtOH, catalyst separated.
  - Batch TON = 388.

# CNRS-Lyon Developments




| | | CNRS, Lyon |
|---|---|---|
| reactor diameter | *[mm]* | 20 |
| reactor length | *[mm]* | 170 |
| reactor volume | *[$cm^3$]* | 48 |
| $v_L$ x $10^3$ | *[m/s]* | 1.7 - 7 |
| $v_G$ | *[m/s]* | 0.12 - 0.47 |
| pressure | *[bar]* | 10 |
| temperature | *[K]* | 323 - 343 |
| catalyst | - | 1% Pd/C |
| particle diam. | *[mm]* | 2 x (2-7), cylinders |
| reactor/particle diam. | *[-]* | 10 |
| catalyst mass | *[g]* | 24 |
| Palladium mass | *[g]* | 0.2408 |
| 4-NPS concentration | *[M]* | 0.02 |

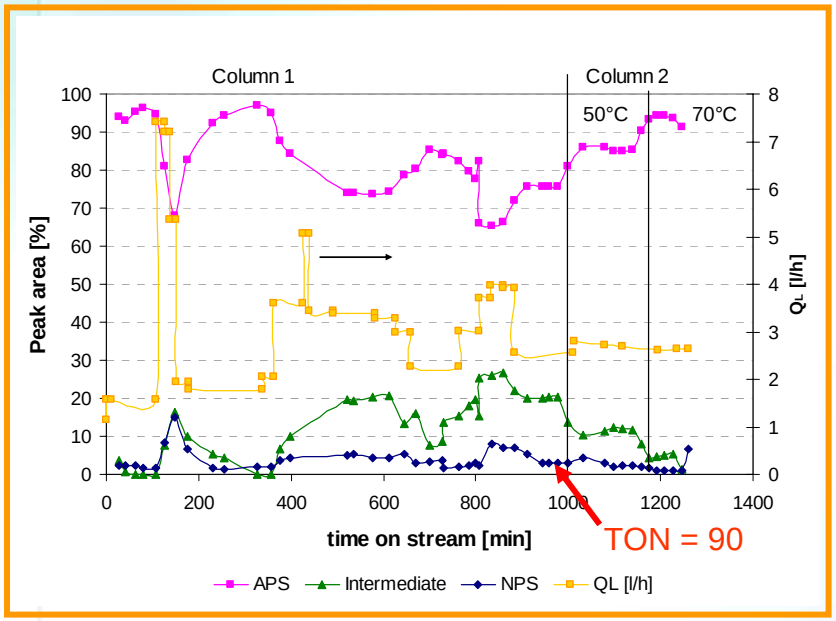
- **Reaction investigated in CSTR & PFR.**
- **Reaction diluted from original batch value of 0.69M to 0.02M to achieve solution chemistry.**
- **Catalyst deactivation observed (as decrease in 4-NPS conversion).**
  - **e.g. 4% conversion decrease at TON=60, 50°C.**

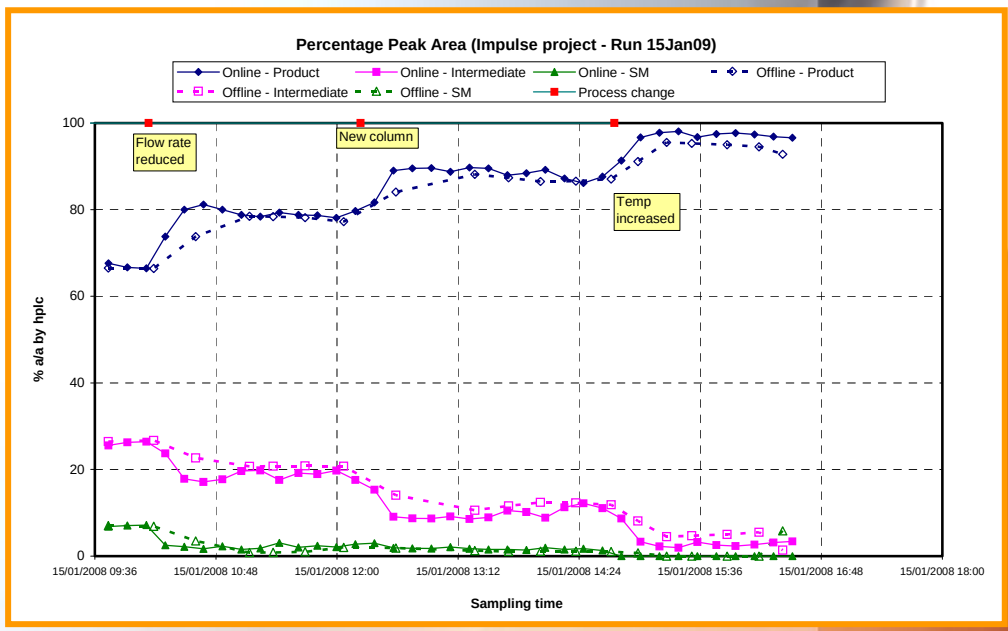
# CNRS-Lyon aq. EtOH Process: Demonstration at GSK

| | | CNRS, Lyon | GSK, Tonbridge |
|---|---|---|---|
| reactor diameter | *[mm]* | 20 | 15.7 |
| reactor length | *[mm]* | 170 | 670 |
| reactor volume | *[$cm^3$]* | 48 | 129 |
| $v_L$ x $10^3$ | *[m/s]* | 1.7 - 7 | 1.6 - 10.6 |
| $v_G$ | *[m/s]* | 0.12 - 0.47 | 0.17 - 0.34 |
| pressure | *[bar]* | 10 | 10 - 40 |
| temperature | *[K]* | 323 - 343 | 323 - 343 |
| catalyst | - | 1% Pd/C | 2% $Pd/Al_2O_3$ |
| particle diam. | *[mm]* | 2 x (2-7), cylinders | 2-4, spheres |
| reactor/particle diam. | *[-]* | 10 | 5.2 |
| catalyst mass | *[g]* | 24 | 61 |
| Palladium mass | *[g]* | 0.2408 | 1.22 |
| 4-NPS concentration | *[M]* | 0.02 | 0.02 |

- **Significant Process Changes**
  - **Different catalyst type at GSK**
  - **Increased Pd mass.**
  - **Increased reactor volume.**
  - **Plant limitations on the $V_G$ flow rate.**
  - **Lower reactor/particle diameter ratio.**

# CNRS-Lyon aq. EtOH Process: Demonstration at GSK




- A range of process parameters investigated.
  - Liquid & gas flow rate, temperature.
- Evidence of catalyst deactivation at TON ~ 90.
- Switch to stand-by column successfully demonstrated.
- On-line hplc data collected, good comparison with off-line results.

# CNRS-Lyon aq. EtOH Process: Conclusions

| reactor | $v_L$ x $10^3$ [m/s] | $v_G$ [m/s] | $T$ [K] | $p$ [bar] | $TON$ [$n_{NPS}/n_{Pd}$] | $LHSV$ [$n_{NPS}/n_{Pd}.h$] | $yield_{APS}$ ($x_{NPS}$) [%] | $r_{NPS}$ x $10^5$ [$mol_{NPS}/g_{Pd}.s$] |
|---|---|---|---|---|---|---|---|---|
| Tonbridge | 2.25 | 0.17 | 323 | 15 | 3 | 2.3 | 94.7 (97.8) | 0.71 |
| Tonbridge | 3.7 | 0.17 | 343 | 15 | 15 | 4.48 | 93.9 (99.0) | 1.17 |
| Tonbridge | 4.7 | 0.17 | 323 | 25 | 53 | 5.7 | 73.7 (95.5) | 1.49 |
| Tonbridge | 3.82 | 0.17 | 323 | 14 | 8 | 4.6 | 84.7 (97.7) | 1.21 |
| Tonbridge | 10.6 | 0.17 | 323 | 34 | 13.7 | 12.9 | 67.9 (84.8) | 3.38 |
| Lyon | 1.72 | 0.47 | 323 | 10 | 50 | 15 | 77.6 (92.3) | 3.86 |
| Lyon | 1.72 | 0.47 | 343 | 10 | 73 | 15 | 85.9 (95.1) | 3.98 |
| Lyon | 6.9 | 0.47 | 335 | 10 | 25 | 75.1 | 70.7 (72.9) | 14.5 |

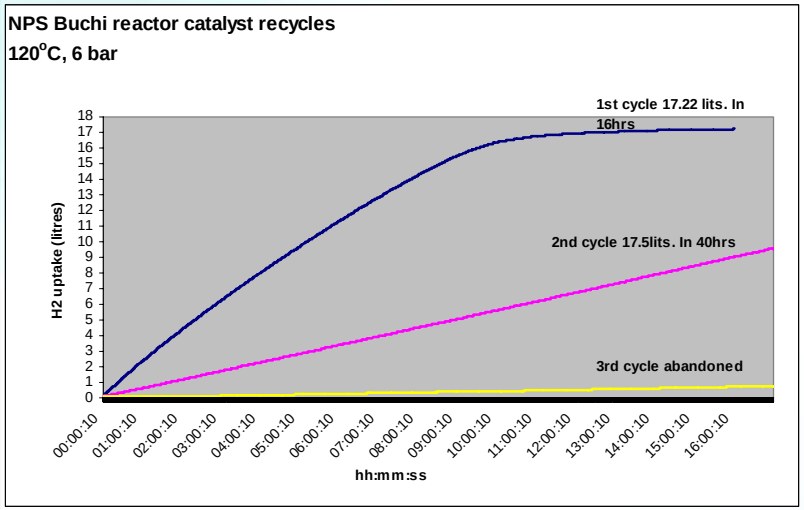
- Hourly productivity lower at GSK demonstration (LHSV):
  - Different hydrodynamic conditions affect mass transfer and/or
  - lower catalyst activity (different catalyst employed).
- Gas flow rate had no impact within the higher pressure range employed at GSK.
- Reactor switch–over demonstrated successfully, demonstrating feasibility to manage catalyst deactivation.

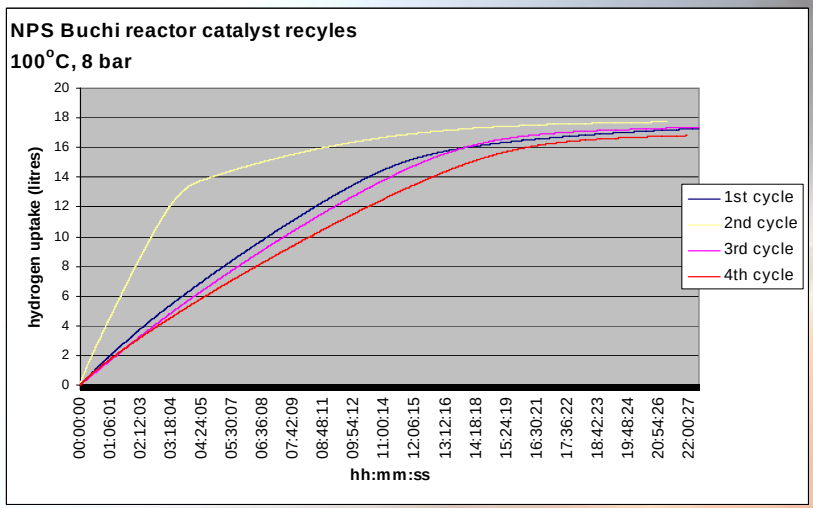
# GSK Process Developments

- **Process development in batch mode:**
  - **2% $Pd/Al_2O_3$ catalyst identified (2- 4mm spheres, suitable for PFR).**
  - **N-methyl pyrrolidinone (NMP) solvent**
    - **Higher 4-NPS input solubility**
    - **Typical working concentration 0.87M (compare 0.02M for aq. EtOH process).**
  - **Process parameters optimised by DoE.**

- **Verification in 2 litre Buchi autoclave.**
  - **Catalyst basket recycle experiments.**

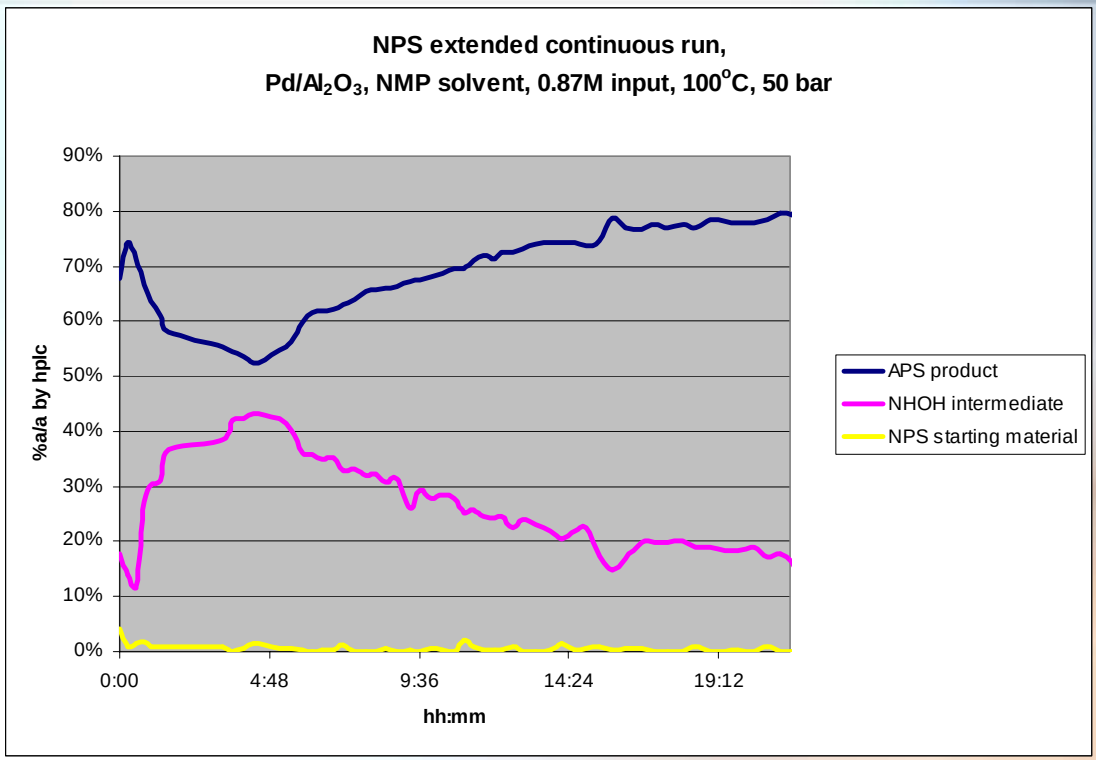
# Catalyst Deactivation in NMP : Batch Mode




- Severe Catalyst deactivation in NMP at 120°C.
  - Complete deactivation on 3rd catalyst cycle.
  - Appears to be coking effect on the catalyst.
- Optimal temperature of 100°C determined.
  - Four catalyst cycles demonstrated.
- Optimal Process conditions were transferred to the continuous mode.

# NMP Continuous Demonstration




- Practically complete conversion of 4-NPS input throughout.
  - Accumulation of NHOH intermediate.
- Conversion to 4-APS product improves as the run progressed.
  - In-line filters were blocking due to particulates.
  - Flow rate fell, reactor residence time increased.
  - Average flow-rate ~2ml/min (LHSV 6.7)
- No indication of catalyst deactivation in duration of run.
- Switch-over to stand-by reactor successful.
  - In-line filter issues terminated the stand-by run prematurely.

# Summary: aq. EtOH vs. NMP process

| | Input conc. (mol/L) | temp (°C) | pressure (barg) | TON | Time on stream (hrs) | Flow rate required to achieve 50g/hr 4-APS output (L/min) |
|---|---|---|---|---|---|---|
| Original Batch Process (aq.EtOH) | 0.69 | 70 - 80 | 1.4 | 388 | 6 | n/a |
| Lyons Continuous Process (aq. EtOH) | 0.02 | 50 - 70 | 10 - 40 | 90 | 17.7 | 0.179 |
| GSK Continuous Process (NMP) | 0.87 | 100 | 50 | 145 | 21.5 | 0.005 |

- **Higher throughput potential with NMP.**
- **No evidence of catalyst deactivation in NMP (at TON 145).**
  - **Known deactivation with aq. EtOH.**

# Conclusions

- The viability of continuous hydrogenation in the pharmaceutical industry has been demonstrated.
- PFR technology allows a simple catalyst management regime to address catalyst deactivation.
- GSK are committed to further evaluation and application of the technology, in order to fully exploit the potential of continuous processing across the emerging portfolio.

# Acknowledgments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