Welcome to IAN SHOTT DEVELOPMENT: A Presentation to ChemSource 2004

Ian Trelfa

24 June 2004

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Ian Shott Development Limited

SEQUENCE - The Steps to Successful Scale-Up

Presented By:

Ian Trelfa
Business Development Manager

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Ian Trelfa – Industry Experience

14 years in the Fine Chemicals Industry.

- 4 years in Process Development.
- 5 years in Production Support.
- 4 years in Project Management.
- 1 year in Business Development.

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Scale-Up from Lab to Pilot Plant Circa 1990

- Receive customer enquiry.
- Search literature and pool ideas based on knowledge and experience.
- Trial small scale preparation using proposed chemical route.
- If chemistry works repeat to confirm product quality.
- Fine tune raw material quantities and solvent volumes.
- Scale up process in laboratory to supply customer sample.
- Offer price and delivery time.
- Obtain purchase order.
- Hold technical/engineering review.
- Prepare product on the plant to meet customer demand.

Scale-Up – The Complete Package Circa 2004

- **S**afety
- **E**nvironment
- **QU**ality
  U
- **EN**gineering
  N
- **C**ost **E**ffectiveness
  E

SEQUENCE – The Steps to Successful Scale-Up.

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From Palmer Research to Ian Shott Development Ltd (1966-2004)

- Founded in 1966 by Dr Derek Palmer.
- One of very first Contract Fine Chemical Companies.
- Close on 40 years experience and involvement in custom synthesis and scale-up.
- Worked with Pharma and Biotech companies to supply grammes to tonnes.
- Gained a reputation as a reliable, competitive custom synthesis partner.
- Has adapted to the market changes and customer demands and expectations.

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SEQUENCE

1. **SAFETY**

- Carry out thermochemical studies on all reactions.
  - Adiabatic.
  - Isothermal.
  - Thermal stability (of intermediates, products, residues, etc.).
- Conduct COSHH Assessments on all reagents.
- Conduct Design and Operability Studies (DOPS).
  - Consider hazards associated with all reagents.
  - Consider incompatibilities of reagent mixtures and materials.
  - Control and operation of the process in the plant.
- Conduct Hazard and Operability Studies (HAZOP'S)
  - Review thermochemistry and safety data.
  - Ensure potential process deviations have been addressed.
  - Determine a basis of safety for all operating steps.
  - Raise actions to address missing data and information.
- UK regulatory bodies expect these Management Safety Systems to be in operation.

Example 1

Fractional distillation of a crude ester at 170°C and 5 mbar with high reflux ratio.

- Thermal stability studies on crude product in the presence of iron showed violent exothermic decomposition at 200°C.
- Risks too high to ignore.

Solutions:

- Discharge residues and decontaminate reactor between batches.
- Conduct iron test on reactor and crude product prior to distillation.
- Connect relief system to a vent down vessel.
- Install high temperature alarm.
- Inert oil quench tank on standby.
- Limit batch size.

Example 2

Lab process which involved a full batch reaction. Starting material, toluene and polyphosphoric acid (PPA) added and heated to 110°C, stirred for 4-6 hrs to complete reaction.

Thermochemistry studies highlighted some serious issues.

- Studies on the reaction mixture showed that at 120°C an exotherm sets in which over time generates a significant amount of heat and pressure.
- Likely to lead to thermal runaway if overheated.
- Unable to engineer a solution – could we change the process?

Example 2 (Continued)

Solutions:

- Added methane sulphonic acid (MSA) to the (PPA) to aid mixing.
- Fed in the starting material as a solution in MSA at 70°C.
- Controlled feed led to instantaneous reaction and low accumulation.
- High and low temperature alarms were installed.
- Agitator failure alarm was installed.
- Hot water rather than steam used to maintain reaction temperature.

Results:

- Process ran well at scale.
- Some added costs were incurred.
- Safety issues were identified and addressed.

2. ENVIRONMENTAL

Considerations to address during laboratory development:-

- Eliminate the use of Class1 solvents.
- Reduce waste and solvent streams by waste minimisation.
- Identify options to effectively control any off-gases.
- Look for more environmentally friendly processes, e.g. biotransformation reactions.

Considerations to address at plant scale:-

- Monitor and analyse off-site aqueous effluent.
- Monitor and analyse emissions from scrubbing towers.
- Consult with off-site waste management specialists regarding waste treatment.
- Offer cleaner solvent waste streams as fuel supports.

New IPPC regulations mean that most of the above are now mandatory.

3. QUALITY

- Meet tighter customer specifications.
- Adopt and implement detailed customer analytical methods of analysis.
- Develop in-house HPLC and GLC methods of analysis.
- Identify and quantify impurities.
- Determine limits of detection of analytical methods.
- Validation of analytical methods of analysis.
- Ensure material passes specification prior to release.

3. QUALITY (Continued)

- Provide competent points of contact:
  - Commercial
  - Project Leader
  - Technical
- Responsive to customer demands and issues.
- Communicate clearly and establish a good working relationship.
- Speed of response is essential to maintain reputation.
- Quality should cover the complete service to the customer.

4. ENGINEERING

- A solution to process problems and issues.
  - Problems presented by Thermochemistry studies.
  - Problems presented by the Process itself.
- Ensure the most appropriate ‘Basis of Safety’ during HAZOP.
- We ask “What if?”
  - Too much, too little.
  - Too high, too low etc.
  - Design of Experiments (DoE’s).

4. ENGINEERING (Continued)

- Determine Best Means of Control.
  - Vent sizing.
  - Pumped feeds, sized orifice plates.
  - Controlled heating and cooling systems.
  - High/low temperature alarms.
  - High/low level alarms.
- Incorporate market developments in Equipment and Technology.
  - In line filtration.
  - Impregnated carbon filters.
  - Powder transfer charging systems.

5. COST EFFECTIVENESS

- Important to select the best synthetic approach and technology.
- Continuous process improvement by Development and Innovation.
- Look for cost improvements at all times.
- Crucial to be ‘Right First Time’.
- Use a flexible costing model.
- Price is often everything to the customer.
  - Long term price may be more important than short term price.
  - Accept realistic margins.

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