



NAVIN FLUORINE
INTERNATIONAL LIMITED



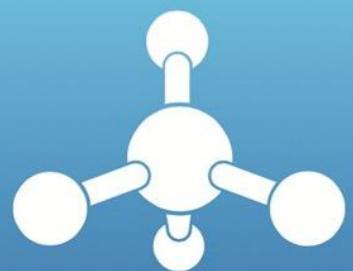
PADMANABH
MAFATLAL
GROUP
Creating value. Sharing value



Milligram to
Multi-tonne
Production



Responsible Care®
OUR COMMITMENT TO SUSTAINABILITY

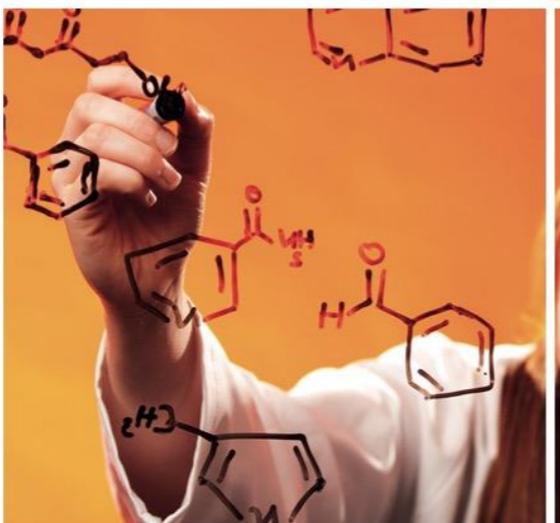
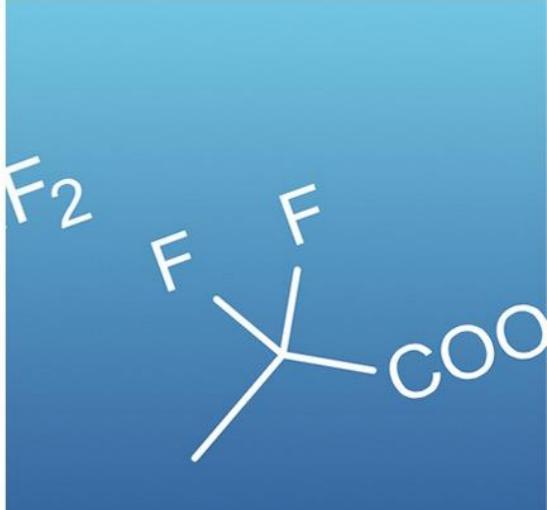
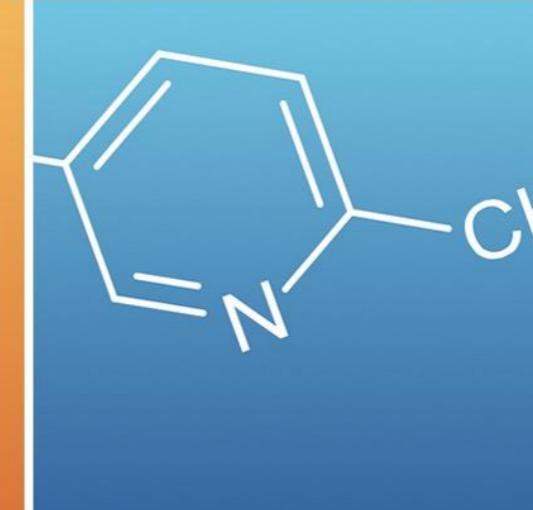


MANCHESTER
ORGANICS

cGMP
Process
Development

9

F
Fluorine
19



Custom
Research &
Manufacturing



Company Presentation

Navin Fluorine: Who are we ?



- Founded in 1967, and part of renowned Padmanabh Mafatlal Group
- India-headquartered, publicly traded company.
- Four business units: Refrigeration, Inorganic Fluorides, Specialty Fluorochemicals, Contract manuf.
- Products on commercial scale include BF_3 , HF, KF, benzotrifluorides
- Custom Research & Manufacturing business unit commenced in 2011 in Dewas, India.
- Pilot plant and R&D laboratories opened in 2010, focused on SF_4 fluorination
- Two GMP Buildings operational and third now approved (2018)



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NFIL At A Glance



NAVIN FLUORINE INTERNATIONAL LIMITED



R 22,
R 134 etc



HF, HF Adducts
KF, ABF, NaF etc



Fluro-containing
Pharma and Agri
Intermediates
 BF_3 and its adducts



Custom Services
from mg to multi
ton-level.

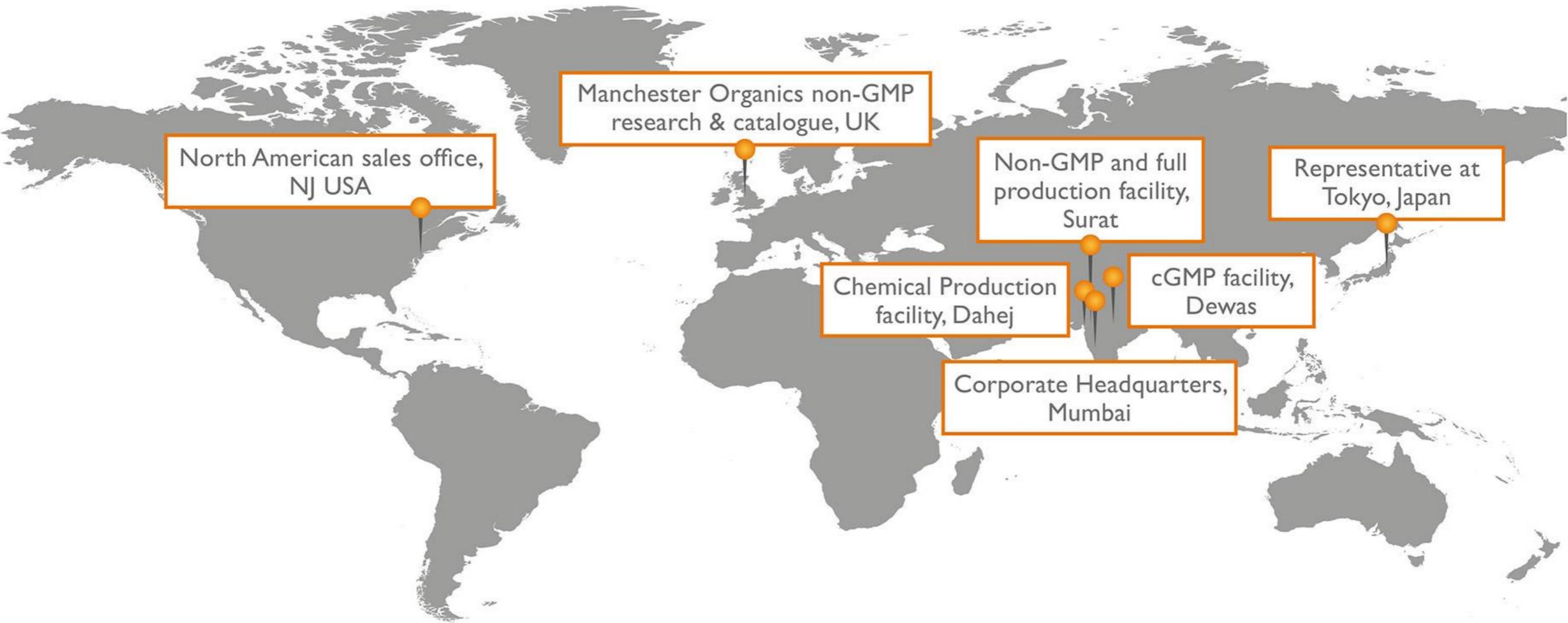


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PADMANABH
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Global Presence - Locations



Over 600 Employees worldwide, with more than 200 scientists

R&D and Manufacturing: Runcorn, UK



- 55 Fume hoods across 6 laboratories.
- High pressure chemistry facility including fluorination, carbonylation, and hydrogenation.
- Vessel size up to 20 L (glass & stainless steel).
- Analytical capabilities include NMR (400 MHz), FT-IR, HPLC, GC, and titrimetry (including KF).

R&D Operations: Dewas, India



- Various synthetic laboratories with 2,500 m² laboratory space.
- Dedicated area with 2 x 5 L and 2 x 25 L autoclaves.
- In-house calorimetry capabilities (HEL Phi-Tec I calorimeter).
- Analytical development laboratory including NMR, FT-IR, UV-VIS, GC, GC-MS, HS-GC, HPLC, HPLC-MS, UPLC, titrimetry, and coulometric KF.
- R&D facilities on same site and in proximity to manufacturing plants.



GMP Pilot Plant: Dewas, India



- Pilot plant with reactors from 50 L to 500 L.
- Glass-lined, stainless steel 316, Hastelloy C-276, and Inconel reactors.
- Total reactor capacity of 10 kL.
- Stainless steel 316 fluorination and hydrogenation autoclaves from 100 L to 650 L - pressures up to 40 bar - with work-up capacity up to 2,000 L.
- Total autoclave capacity of 1,150 L.
- Multiple solids isolation and drying capabilities.
- Distillation section and separate liquids packaging.



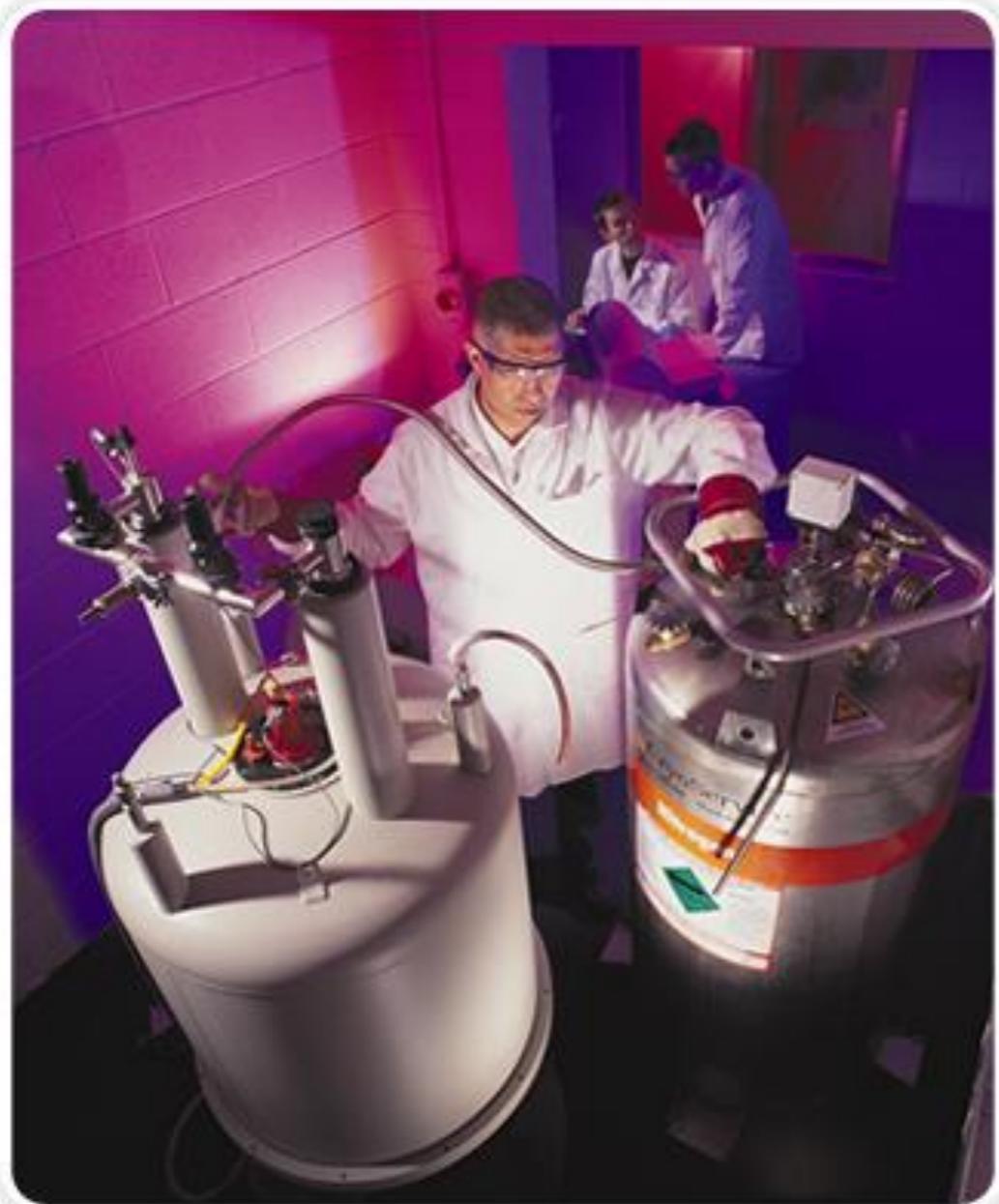
GMP Production Plant: Dewas, India



- Manufacturing plant with reactors from 500 L to 7,000 L.
- Glass-lined, stainless steel 316 L, and Hastelloy C-276 reactors.
- Total capacity is 50 kL.
- Stainless steel fluorination and hydrogenation autoclaves from 1,000 L to 2,000 L - pressures up to 40 bar - with work-up capacity up to 3,000 L.
- Total autoclave capacity of 4,000 L.
- Multiple solids isolation and drying capabilities.



Quality control: Dewas, India



- Chromatographic capabilities include GC, GC-MS, HS-GC, HPLC-MS, and UPLC.
- Spectrometric techniques comprise NMR (300 MHz), UV-VIS, FT-IR.
- Wet chemistry capabilities.
- Coulometric KF capabilities
- Muffle furnace.
- Microbiology laboratory.

Expansion Plans: Dewas, India



- Board approval for significant expansion of current GMP facility in Dewas given February 2018.
- Multi-tonne, multi-purpose plant scheduled for commissioning by June 2019.
- Reactor capacity up to 10,000 L with maximum operating pressure of up to 80 bars
- New plant will have total working capacity of approximately 100 kL.
- Bank of 6 to 8 1,000-1,500 L fluorination reactors
- Plant will be cGMP and statutory requirement compliant.
- All regulatory and license clearances in place



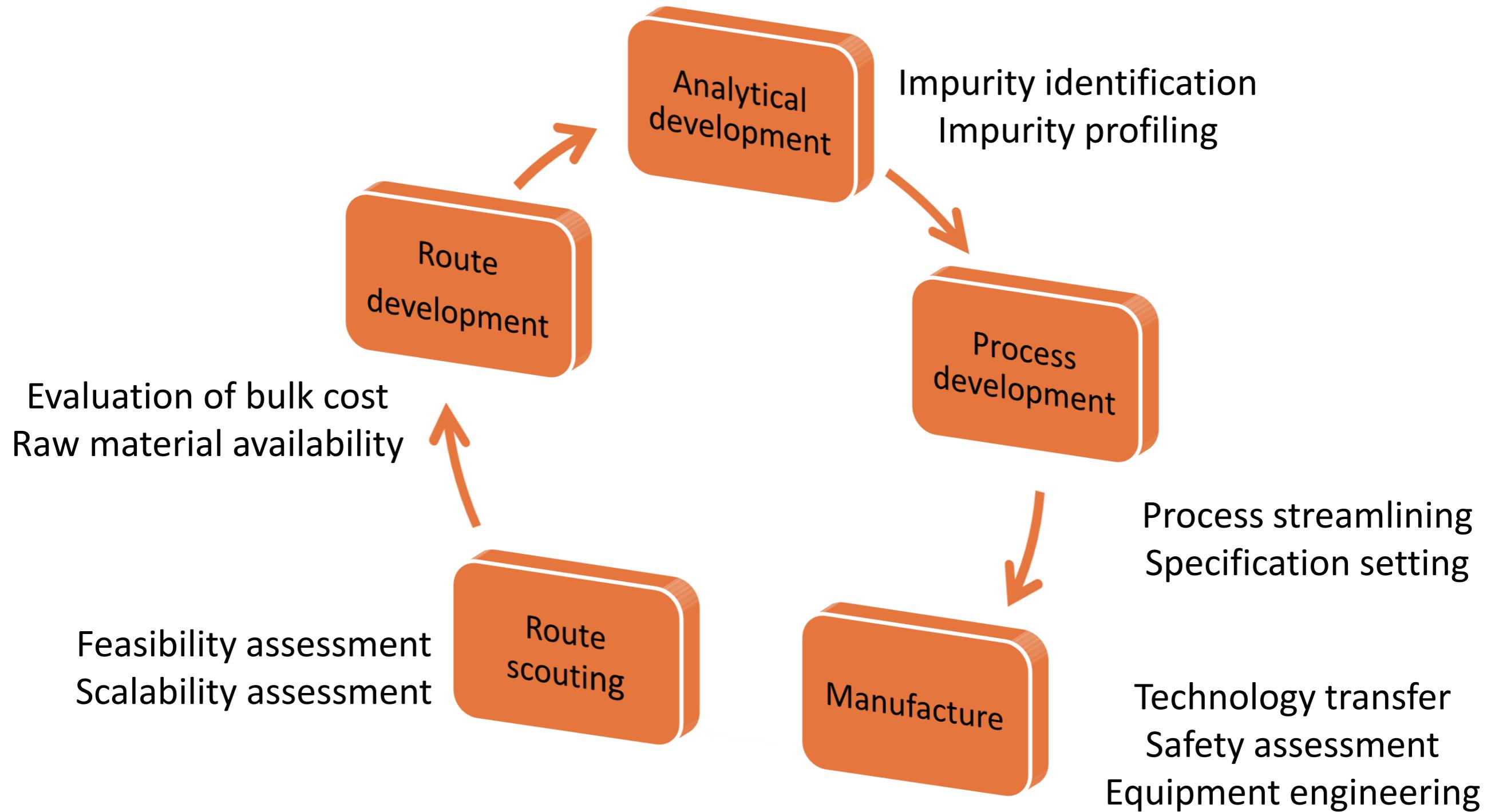
Expansion Plans : Dewas, India

- The facility will accommodate 30 plus reactors
 - (SS, MSGL, Hastelloy & High pressure)
 - Distillation section
 - Powder processing area
 - All required utilities, ancillary functions expansion (warehouse, ETP, OHC)
 - QC expansion with addition of PR&D and AR&D labs for CRO work
 - New administration and technical building

Expansion Plans : Dewas, India

- Expansion include a Process Safety Lab covering all aspects from early development, process optimization and manufacturing
 - ❖ DSC/TSU, ARC for thermal screenings, reaction calorimeters, minimum ignition energy/temp. apparatus, layer ignition temp, impact sensitivity /electrical resistivity tests, charge decay analyzer, burning behavior and liquid conductivity tests apparatus
- Expansion includes a Kilo Lab with dedicated personnel
 - ❖ 20 L & 50 L reaction assemblies
 - ❖ Dryers, distillation & purification set ups

From Chemical Structure to Process

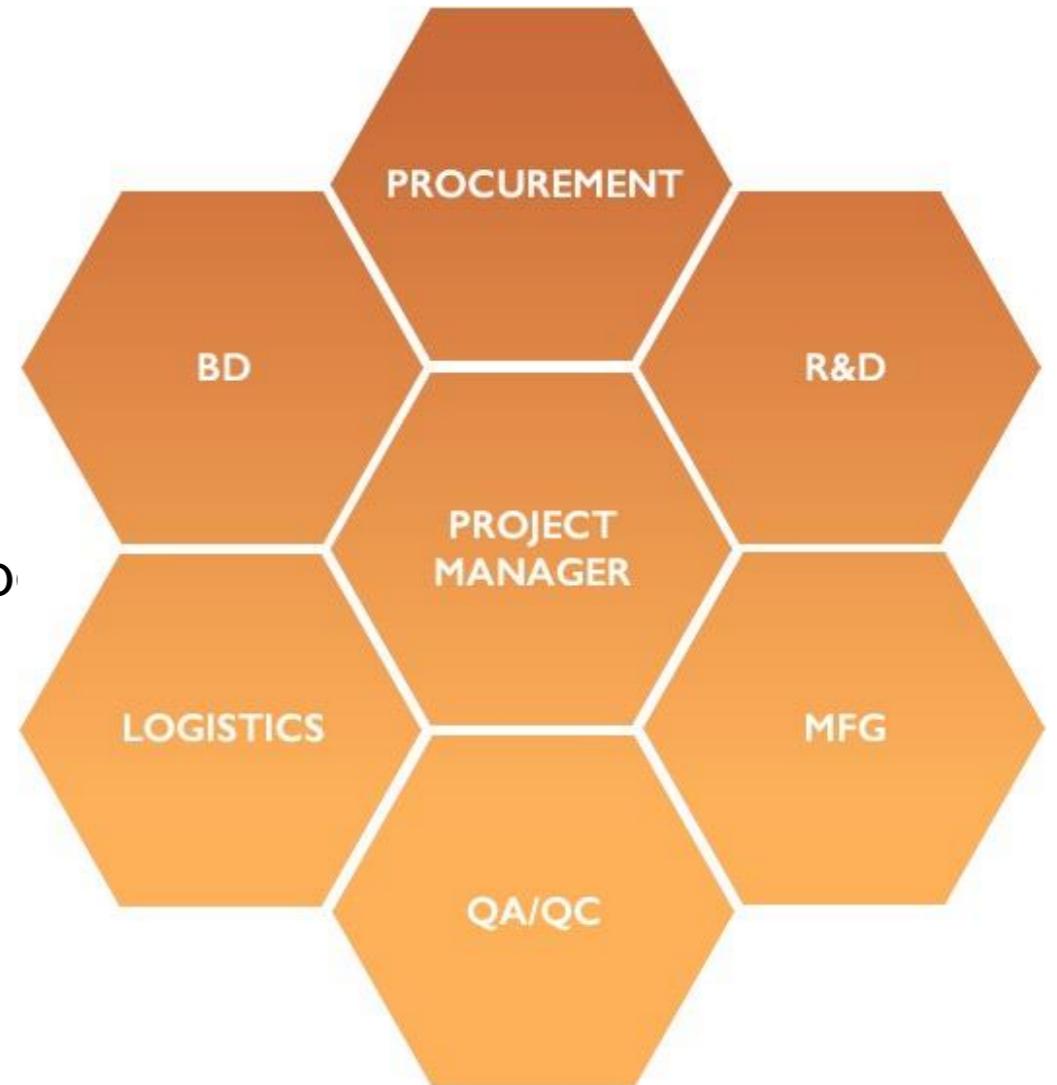


Process Research & Development

- Expertise in both Europe and India
- Flexible business model including FTE-type contracts
- Efficient technology transfer directly from Manchester/Dewas R&D laboratories to pilot plant and then on to production plant
- Development and scale-up of fluorination chemistries at high pressures to GMP
- Development and scale-up of high pressure chemistry up to 100 bar
- Evaluation of process safety – DSC / Adiabatic calorimetry on site
- Separate analytical lab dedicated to supporting process development

Project Management

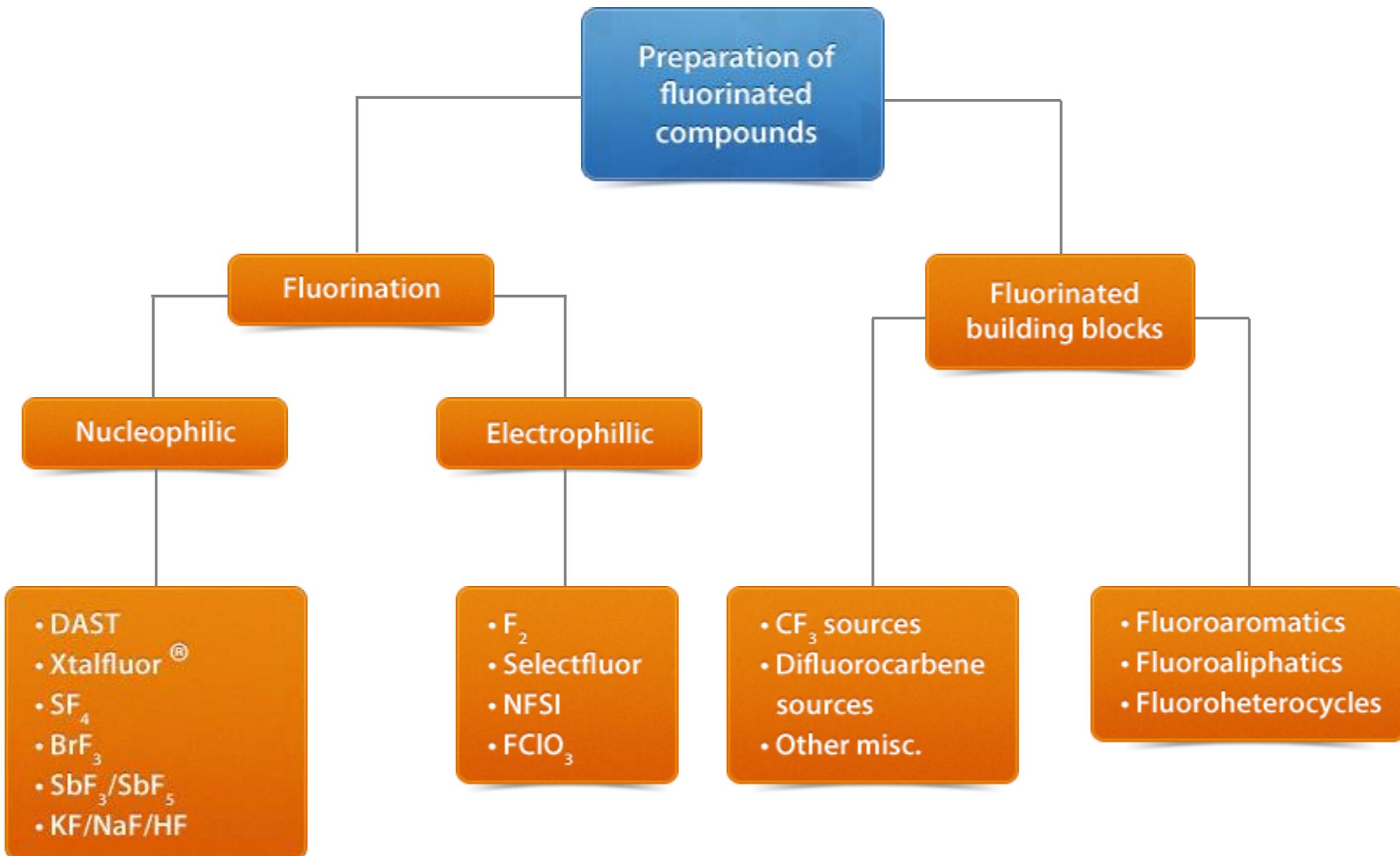
- Project manager assigned early at quoting stage
- Manages internal functions, both in UK and India
- Has full handle on all technical aspects of the project
- Works closely with assigned BD – Client is key contact point
- Provides regular updates tailored to needs of client
- Manages the project from start to successful completion



Chemistry Processes Offered

- Acylation
- Alkylation-liquid & vapor phase
- Bromination & chlorination
- Side chain chlorination
- Fluorination - both liquid & vapour phase
- Nitration
- Reduction
- Catalytic Hydrogenation
- Hydro-dehalogenation
- Fries Rearrangement
- Esterification
- Claisen's Condensation
- Diazotization
- Hydrolysis
- Oxidation
- Ammonolysis
- Deamination
- Grignard's Reactions
- Cyanation
- Halex Reactions

Fluorination Strategies



Scalability of nucleophilic fluorination methods



Fluorination type	Method	Scale-up at Navin	Main concern
Deoxofluorination	Sulfur tetrafluoride	Yes	
Deoxofluorination	XtalFluor(-E or -M)	Yes	
Deoxofluorination	DAST or Deoxo-Fluor	No	Thermal stability
Deoxofluorination	Phenofluor	No	Availability and price
Halex	KF	Yes	
Halex	CsF	Possible	Price
Halex	Bu ₄ F (anhydrous)	Possible	Price
Balz-Schiemann	NaNO ₂ , HBF ₄	Possible	Safety
Balz-Schiemann	<i>tert</i> -butylONO, HF-pyridine	Yes	

Scalability of electrophilic fluorination methods

Fluorination type	Method	Scale-up at Navin	Main concern
Fluorination	Fluorine	No	Safety
Fluorination	Trifluoromethyl hypofluorite	No	Safety
Fluorination	Acetyl hypofluorite	No	Safety
Fluorination	Perchloryl fluoride	No	Safety
Fluorination	Xenon difluoride	Possible	Price and availability
Fluorination	NFSI	Yes	
Fluorination	Selectfluor	Yes	
Fluorination	<i>N</i> -Fluoropyridinium sulfate	Yes	

Scalability of trifluoromethylation methods and building block approach



Fluorination type	Method	Scale-up at Navin	Main concern
Trifluoromethylation	Trifluoroacetic acid derivatives	Yes	
Trifluoromethylation	MFDA	Yes	
Trifluoromethylation	TMSCF ₃ /TESCF ₃	Yes	
Trifluoromethylation	Umemoto reagents	No	Availability and price
Trifluoromethylation	Togni reagents	No	Safety
Trifluoromethylation	Shibata reagents	No	Availability and price
Trifluoromethylation	Trifluoromethylator™	No	Availability and price
Trifluoromethylation	Potassium trimethoxy-(trifluoromethyl)borate	No	Availability and price
Difluoromethylation	TFDA/MFDA	Yes	
Difluoromethylation	(Difluoromethyl)trimethylsilane	Yes	
Difluoromethylation	Difluoromethyl triflate	Yes	
Building block	Various	Yes	

Non-fluorination Chemistry



Rearrangement

Hydrolysis
Carbanion
Ammonolysis
Alkylation
Hydrodehalogenation
Condensation
Bromination
Esterification
Reduction
Organometallic
Cyanation
Deamination
Acylation
Mitsunobu
Crosscoupling
Chlorination

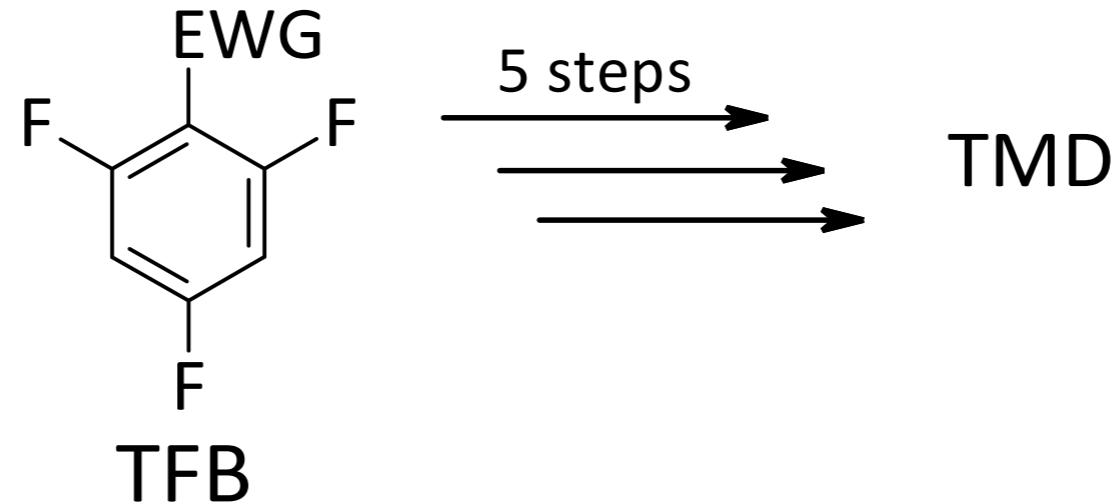


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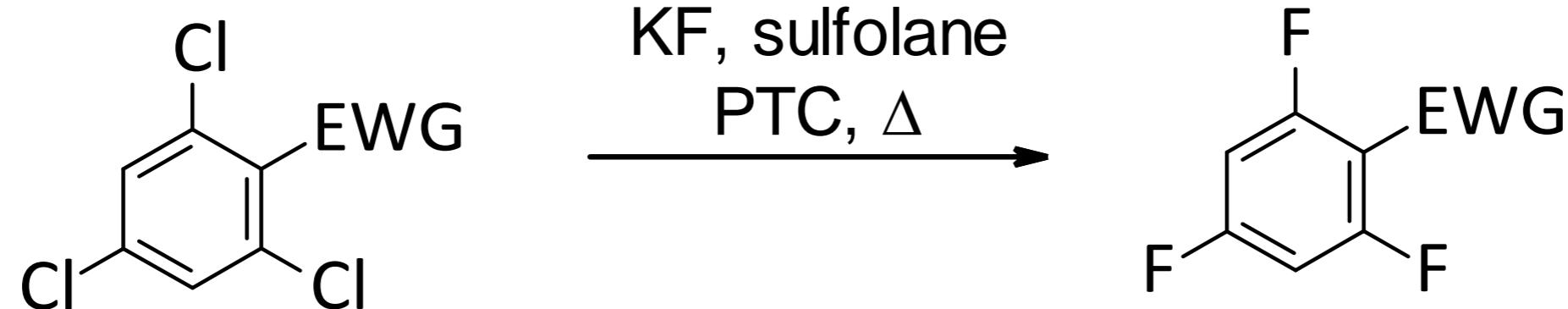
Case study: Back integration of fluorinated building block



Development of a process from cheap commodity was desired to strengthen supply chain for key starting material, reduce exposure to China, and bring fluorination in house.

Seven different routes using starting materials available in bulk were identified

Case study: Back integration of fluorinated building block



- One route was identified as the most cost-effective option.
- Process optimisation was performed in-house.
- Technology transfer of process to established partner for toll manufacturing of chlorinated intermediate.
- In-house Halex conversion of chlorinated intermediate to fluorinated intermediate.

Case study: Back integration of fluorinated building block

End 2015

September
2016

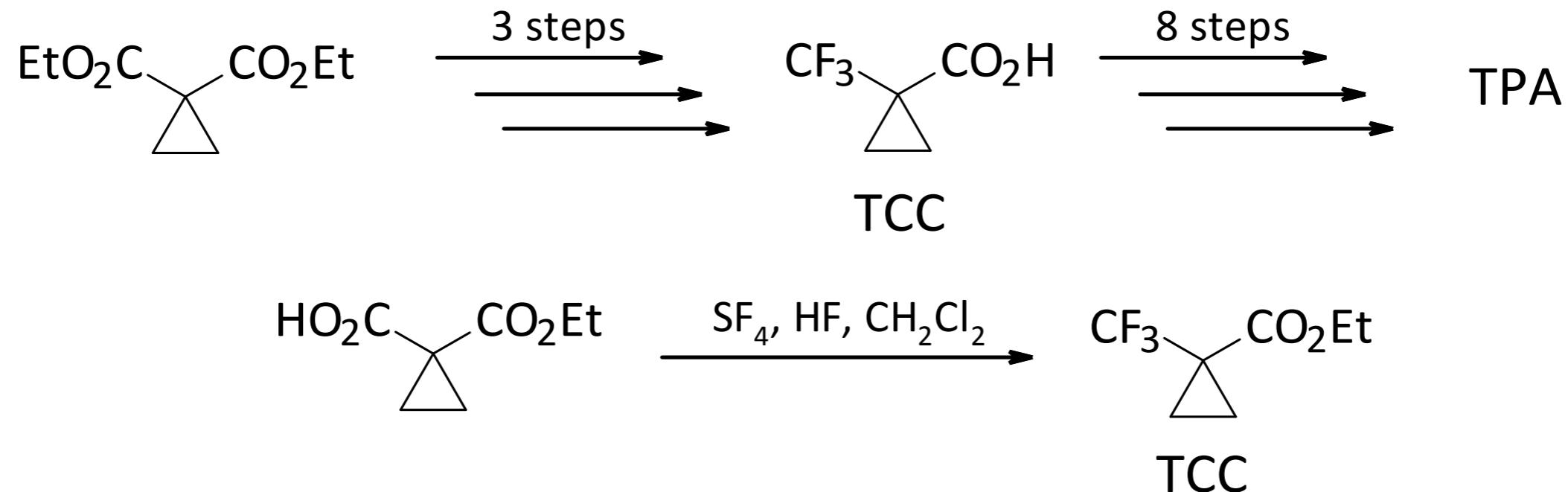
Second
half 2016

December
2016

January
2018

- Process technology transfer from customer.
- Delivery of 150 kg TMD from purchased TFB.
- Six month programme for route scouting, optimisation, PR&D, and piloting for TFB.
- Delivery of 3 MT TMD from purchased TFB.
- Delivery of 8 MT TMD from split supply: 2.5 MT TFB purchased from China and 3.8 MT locally produced. Toll manufacturer converted 7 MT 1,3,5-trichlorobenzene to 7 MT 2,4,6-trichlorobenzonitrile, which was converted in-house to 3.8 MT TFB.

Case study: Deoxofluorination downstream chemistry



- TCC is a Navin in-house product.
- Fluorination step involves deoxofluorination with SF_4 .
- Downstream chemistry involves non-fluorination chemistry (reduction, FGI, Mitsunobu coupling, and deprotection)
- Heterocyclic building block not available on bulk and (two-step) process developed from scratch with approx. 1 MT production in 2017.

Case study: Deoxofluorination downstream chemistry



**Mid
2015**

Three-step fluorinated building block already transferred to manufacturing site for large-scale production (>100 kg batches).

**Early
2017**

Downstream chemistry transferred to manufacturing site with development work, 1 kg demonstration batch, and 5 kg piloting campaign completed in 4 months.

**First half
2017**

First bulk campaign furnishing 64 kg final material completed in 4 months with maximum 24 kg batch size for TPA.

**First half
2017**

Follow-up campaign of 225 kg final material with 75 kg batch size for TPA.

2018

Manufacturing campaign of 1.2 MT TPA in progress.



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Case study: We also do non-fluorinated chemistry!



Delivery of 55 kg late-stage intermediate

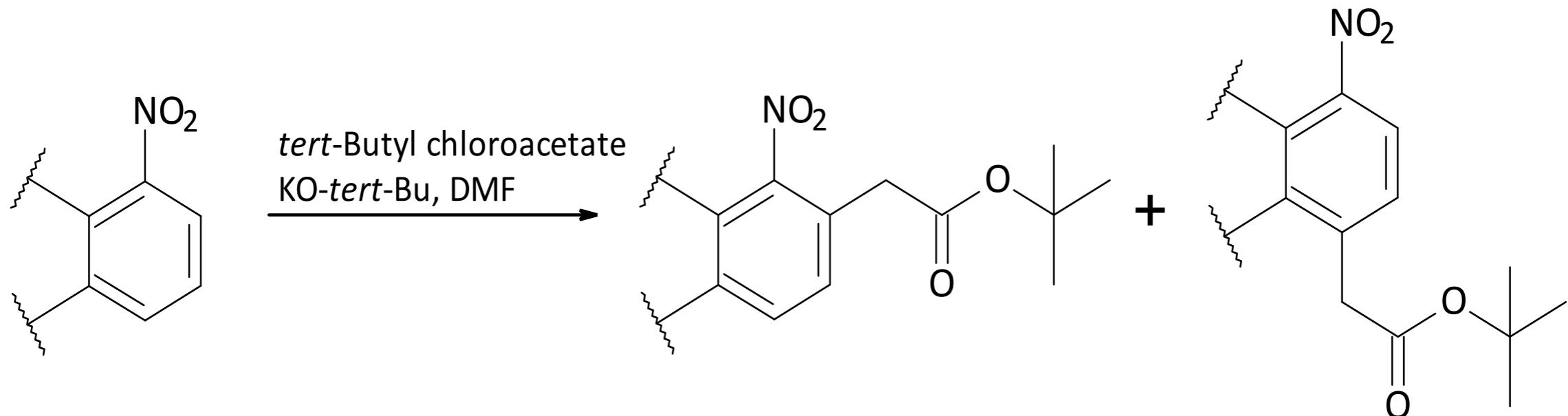
Existing process comprised six separate stages

Chemistry involved non-fluorination chemistry

Dilute bottleneck step

Difficult separation of regioisomeric mixture

Case study: We also do non-fluorinated chemistry!



Process improvements

- Simplified work-up procedure.
- Elimination of inefficient slurry procedure.
- Introduction of more efficient slurry procedure in next stage.

Case study: We also do non-fluorinated chemistry!



Overall yield improvement from 6% to 11%

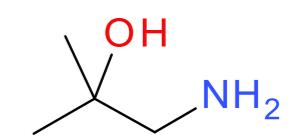
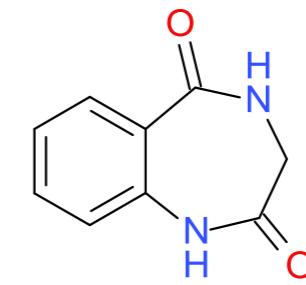
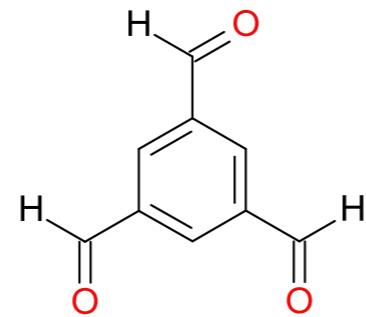
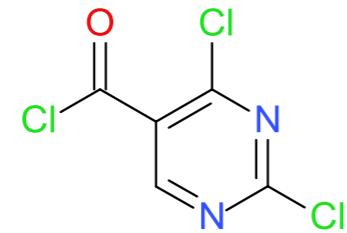
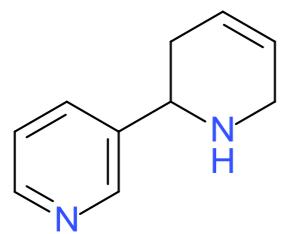
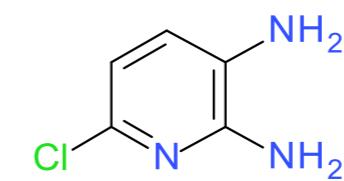
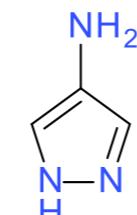
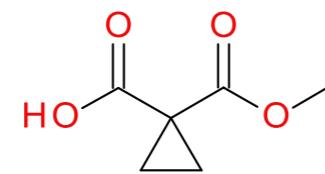
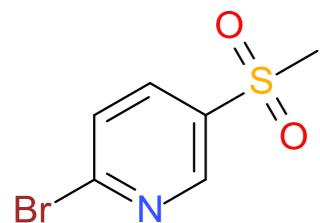
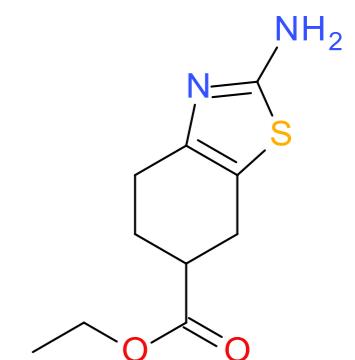
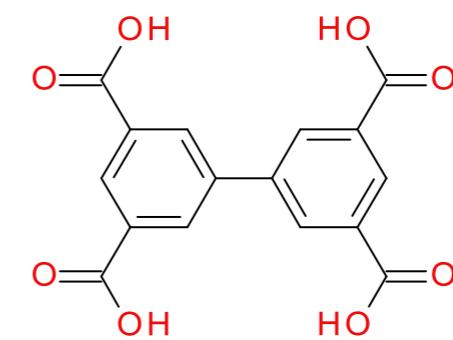
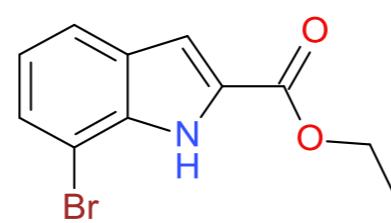
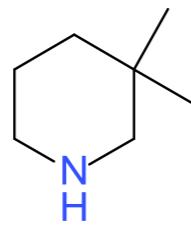
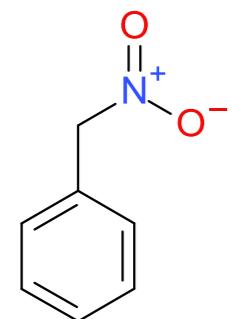
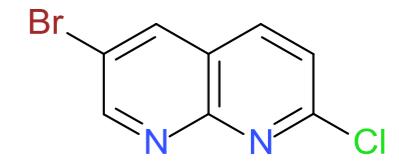
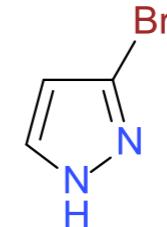
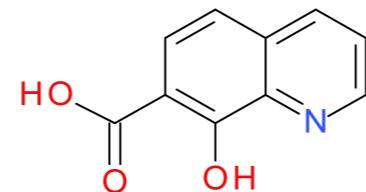
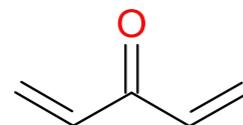
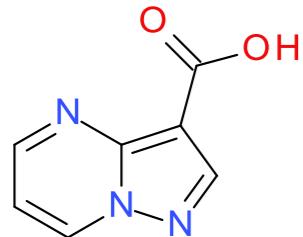
Piloting batch (1 kg) delivered after development work

Delivery of agreed amount with 10% overage

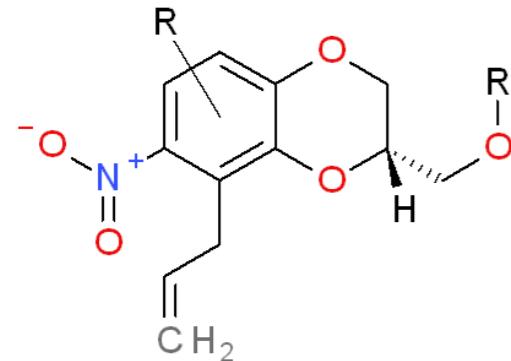
A total of 29 batches were completed in 3½ months

Delivery within originally agreed timelines

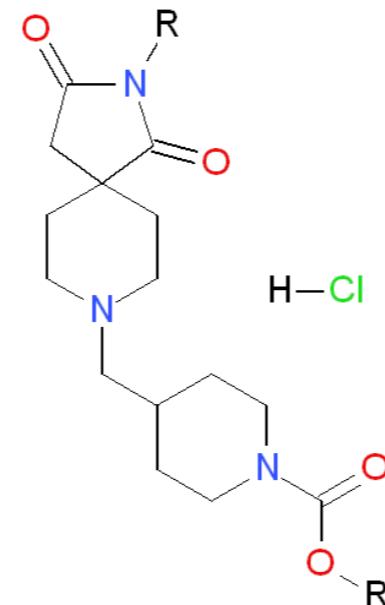
Non-fluorinated building blocks examples:



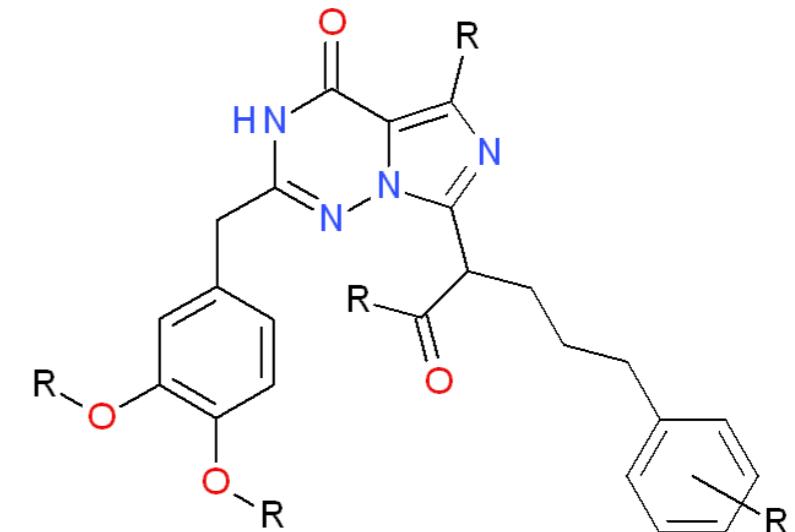
Custom Synthesis - examples



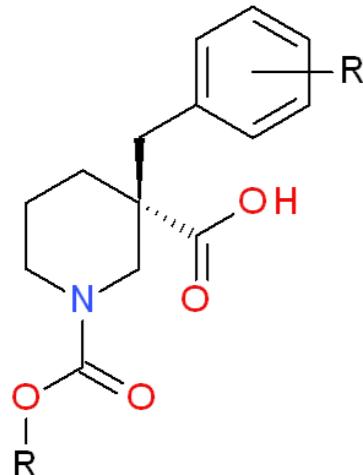
250g prepared, 4 stages



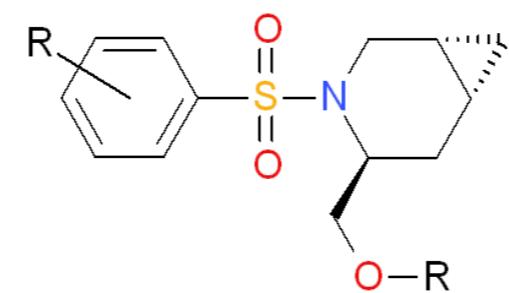
1g prepared, 7 stages



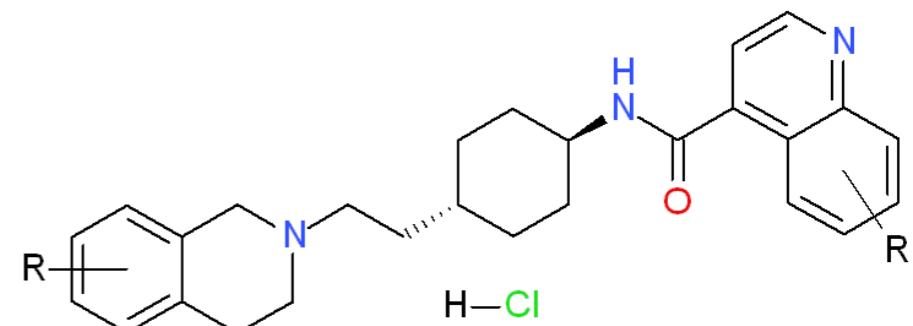
5 g prepared, 7 stages



100g prepared, 3 stages



100g prepared, 8 stages



15g prepared, 14 stages

Health, Safety & Environment

- Site specific safety protocols
- On-site fire station, medical centre & 24 hour security
- Effluent treatment plant to eliminate need for off-site waste disposal
- Comprehensive staff training programs
- Responsible care certification – from September 2014
- ISO 9001/14001/18001 accredited firm
- Regular audits/assessments by global companies
- Passed cGMP audits by major pharma clients

Why us?

- Core expertise in pressure chemistry & fluorination – commercial SF₄ fluorination
- Diverse range of chemistries offered
- Highly experienced team, with effective project management
- Established company, with both UK/India locations. Supply chain security
- Continued investment in new equipment & facilities
- Strong commitment to employee health and safety and the environment
- Flexibility of R&D, process development both in UK & India with scale-up
- Successfully audited to cGMP by many global pharma companies



“ Fluorination,
your partner for life.

Thank You



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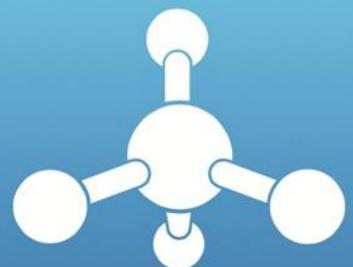
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Creating value. Sharing value



Milligram to
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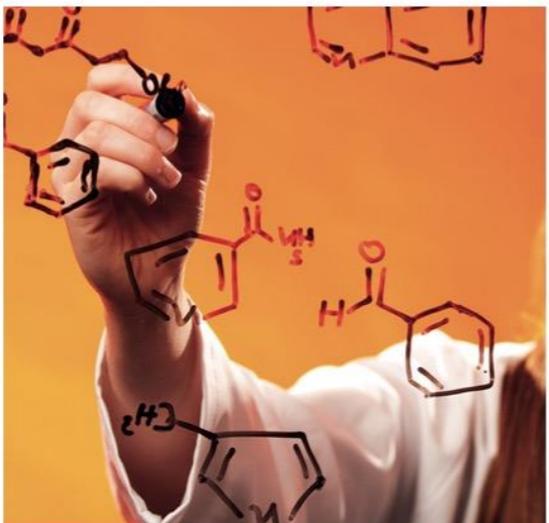


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Process
Development

9

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Custom
Research &
Manufacturing



Thank you