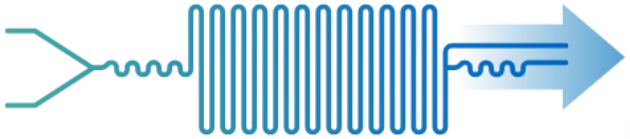
CONTINUOUS MANUFACTURING – CURRENT STATUS AND REGULATORY EXPECTATIONS

22-23 JUNE, 2023



8th GLOBAL PHARMACEUTICAL QUALITY SUMMIT 2023

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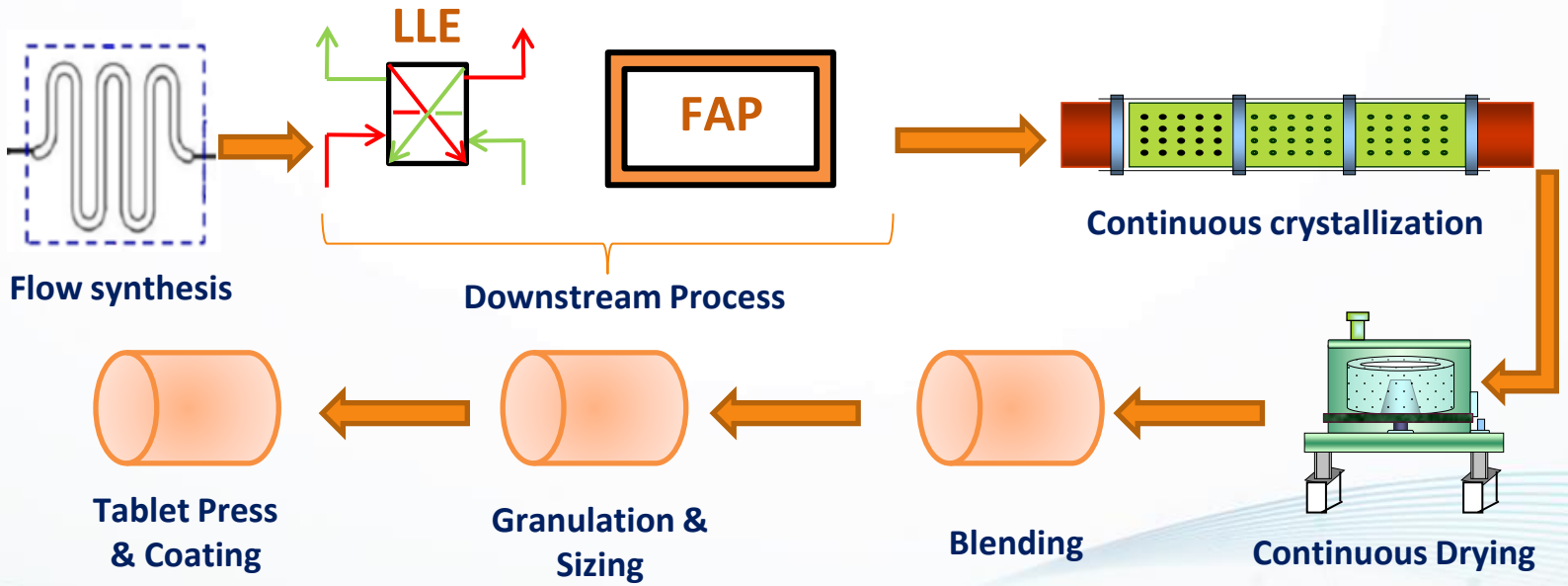
AGENDA

- INTRODUCTION TO CONTINUOUS MANUFACTURING (CM) CONCEPT
- CONTINUOUS FLOW SYNTHESIS IN PHARMA INDUSTRY
- FLOW CHEMISTRY EQUIPMENTS
- CASE STUDIES AND ACHIEVEMENTS – FROM LAB TO PLANT
- ICH Q13: CONTINUOUS MANUFACURING OF DRUG SUBSTANCES AND DRUG PRODUCTS
- EXAMPLES OF DRUG SUBSTANCE AND DRUG PRODUCT CM SYSTEM
- BENEFITS ACHIEVED WITH FLOW TECHNOLOGY
- IMPACT OF CONTINUOUS FLOW MANUFACTURING ON BUSINESS

INTRODUCTION

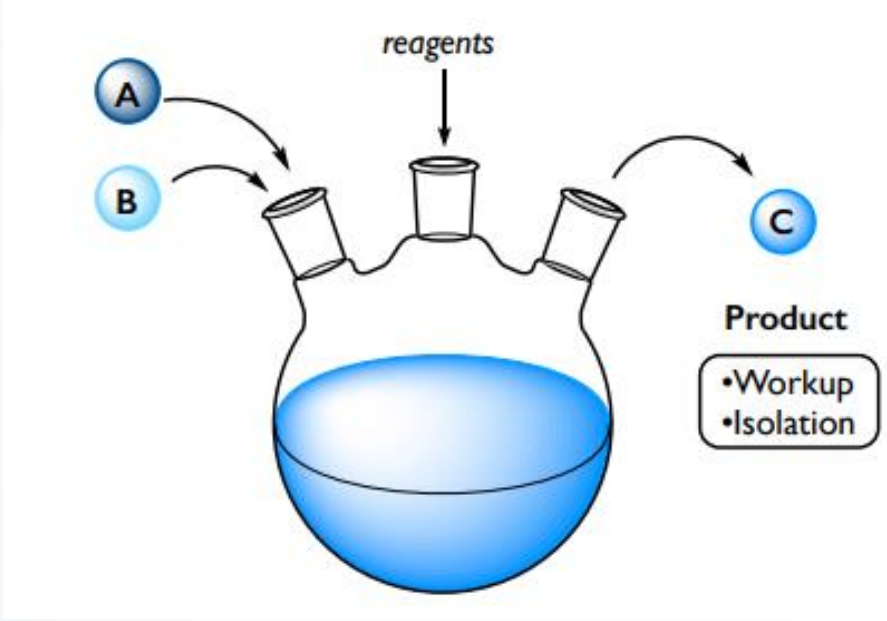
- Pharmaceutical industry since ages have used batch manufacturing which involves large equipment and costly production set up, high quantity of reagent handling, multiple steps and lengthy process of manufacturing.
- Recently, industry has seen a paradigm shift from Batch manufacturing (BM) to Continuous manufacturing (CM) which is much faster, safer and more efficient way.



BATCH *vs* CONTINUOUS OPERATIONS

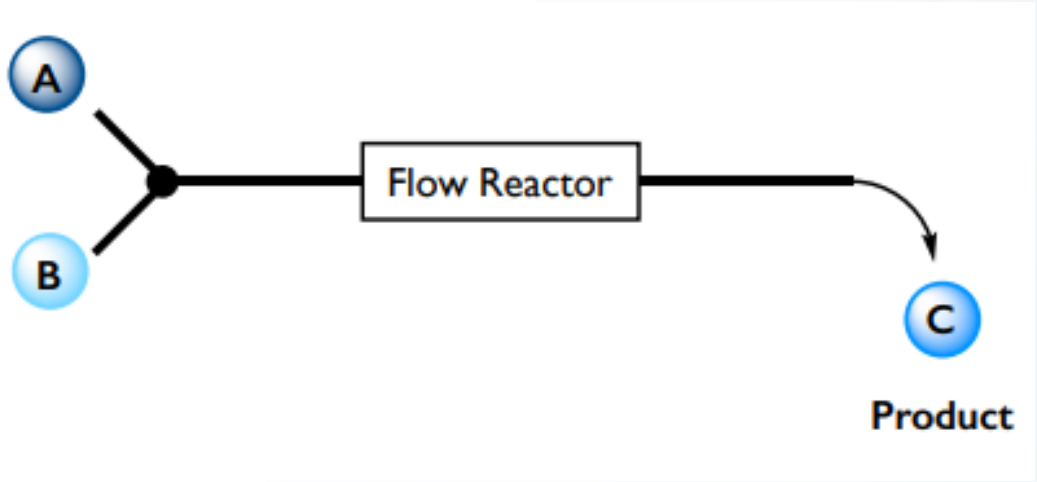
INNOVATION. QUALITY. GLOBAL REACH.

BATCH CHEMISTRY



Reactants added, reacted, and isolated discretely

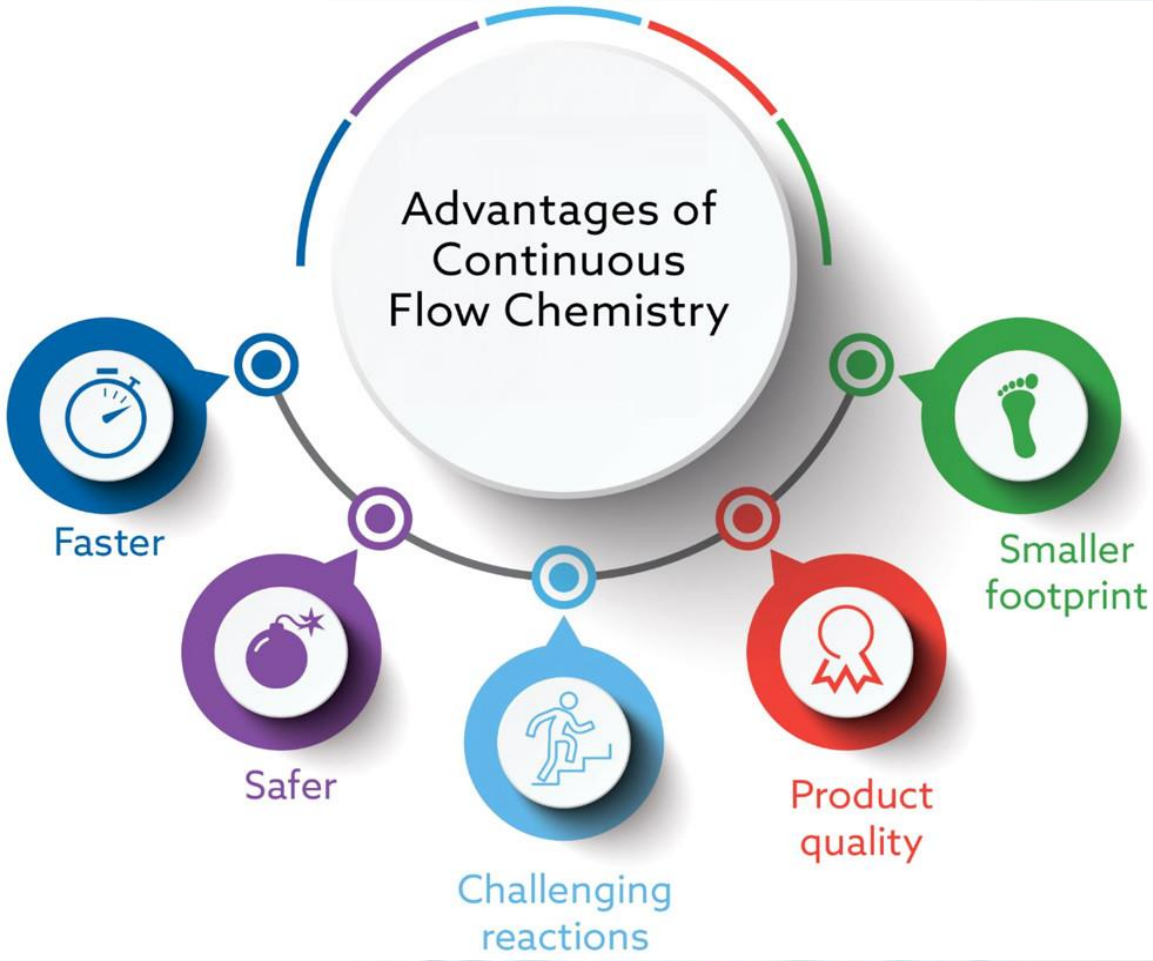
FLOW CHEMISTRY



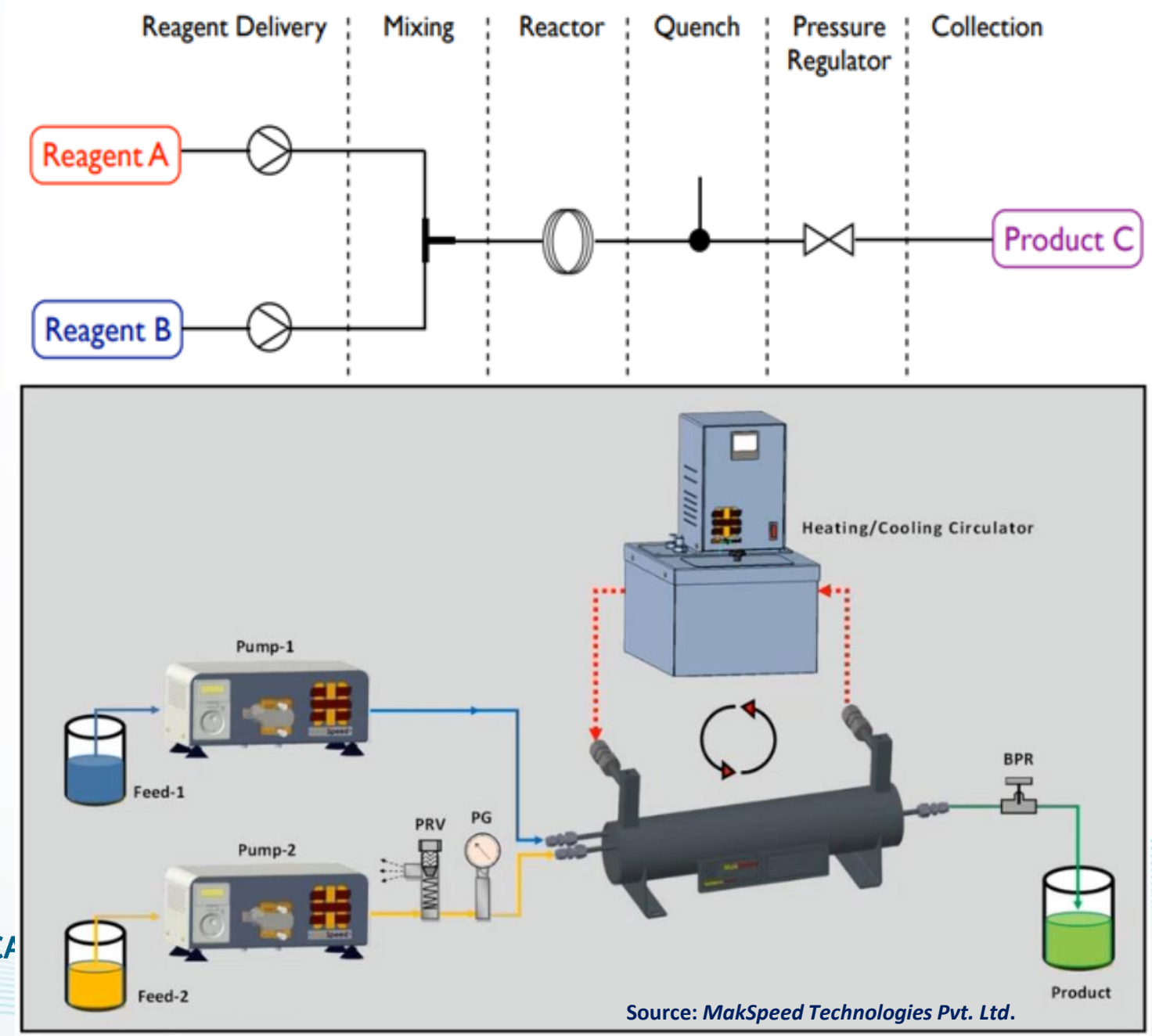
Reactants added, reacted, and isolated continuously

ADVANTAGES OF CONTINUOUS MANUFACTUTRING/FLOW CHEMISTRY

- Heat-transfer coefficient is very high in flow reactors due to high surface to volume ratio which enable intense mixing of reactants in the micro reactor compared to traditional batch reactor.
- Flow provide higher yield and selectivity as well as safer reactions.
- Chemistry which we call forbidden in batch mode can be explored using flow chemistry.



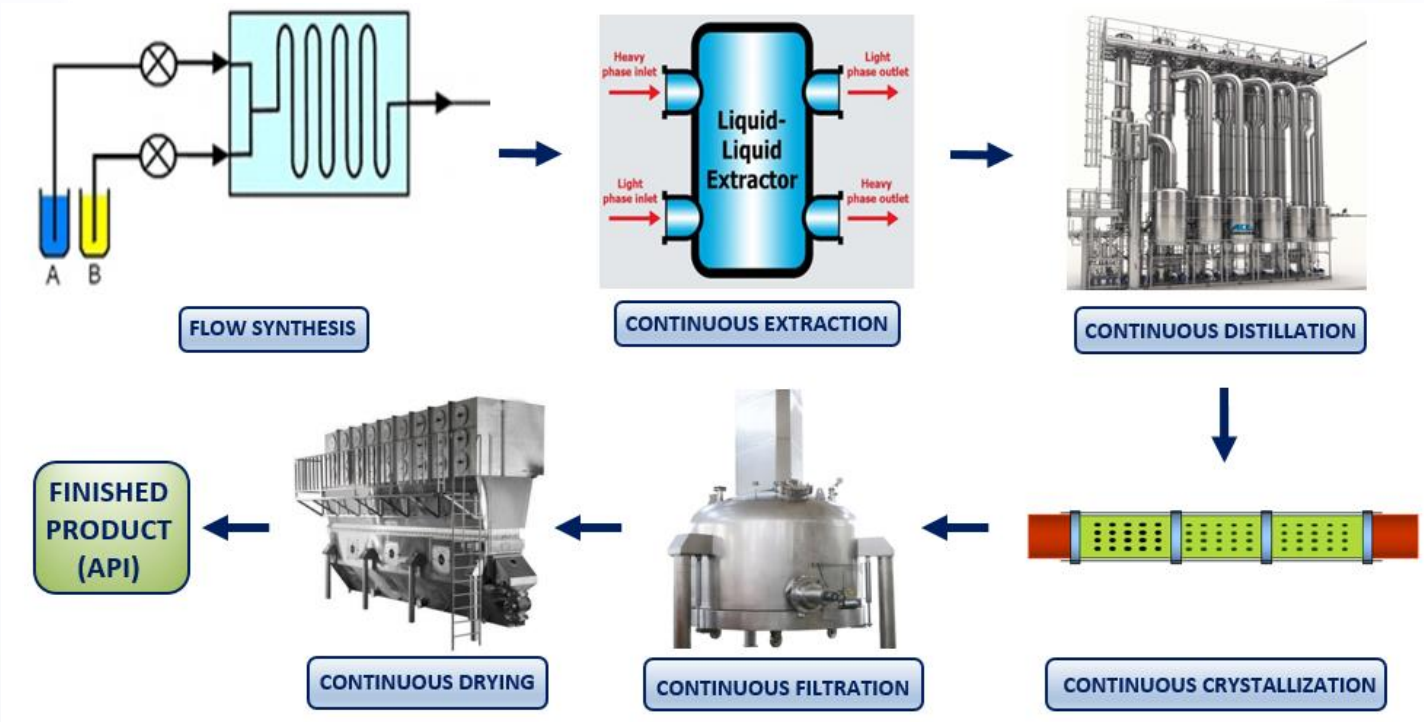
ANATOMY OF FLOW REACTOR SYSTEM



CONTINUOUS FLOW SYNTHESIS IN API/FINE CHEMICALS

CM - Need of the hour ?

- To produce low-cost generic APIs is the need of hour which can not be achieved through backward integration, recovery and recycling of reagents/solvents.
- Integrated continuous manufacturing of API can overcome many of these limitations where upstream and downstream processes are integrated into a seamless process.



INTEGRATED CONTINUOUS MANUFACTURING OF API

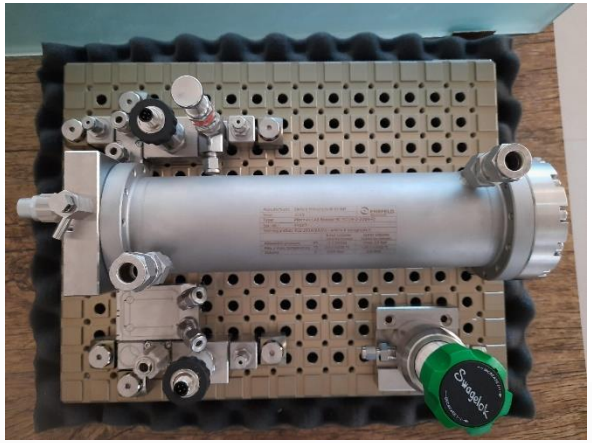
FLOW CHEMISTRY EQUIPMENTS IN OUR LAB

Coflore - Agitated Cell Reactor

Fixed Bed Reactor

Vapourtec E Series

Corning G1 Reactor

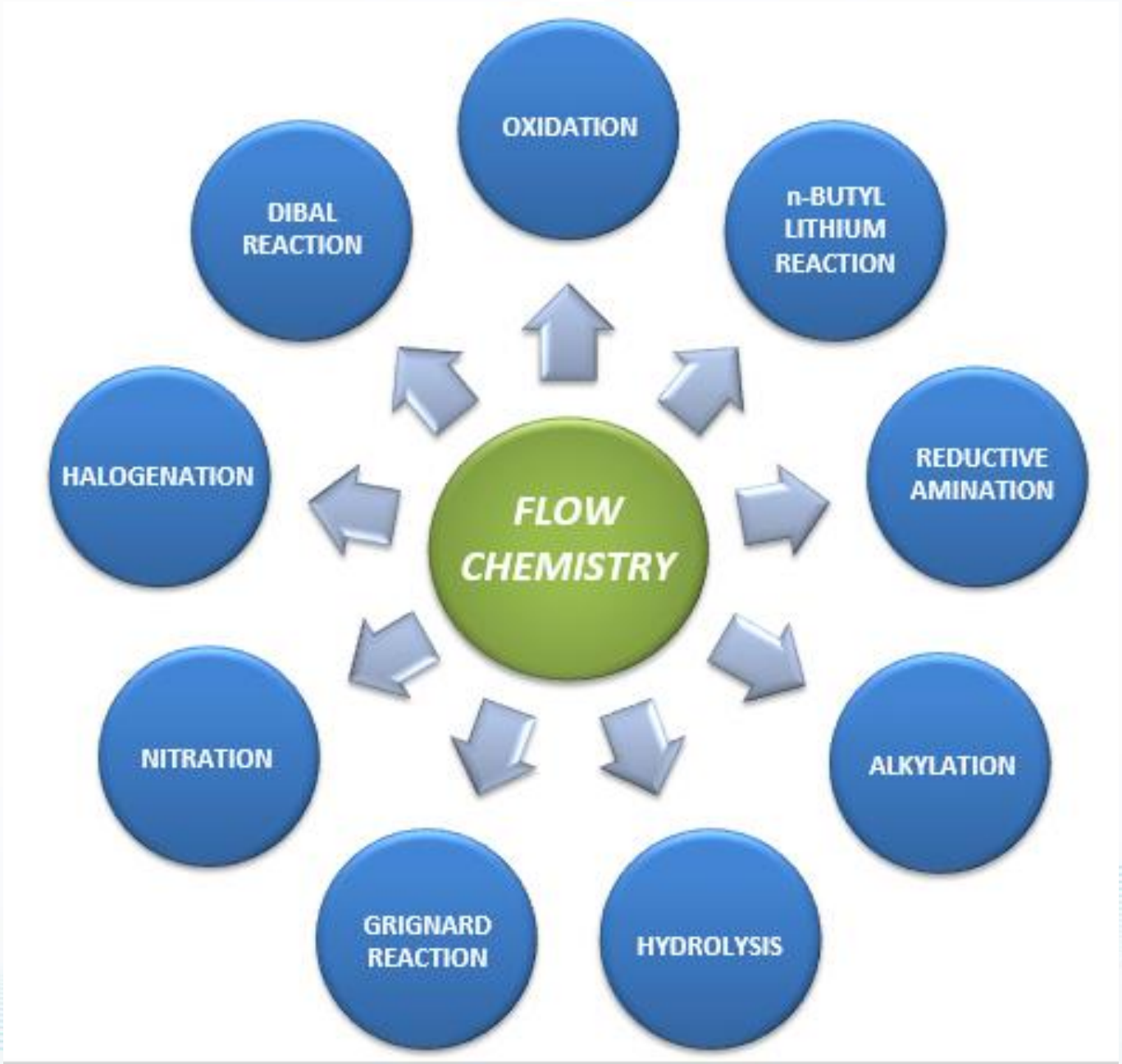


Miprowa Ehrfeld

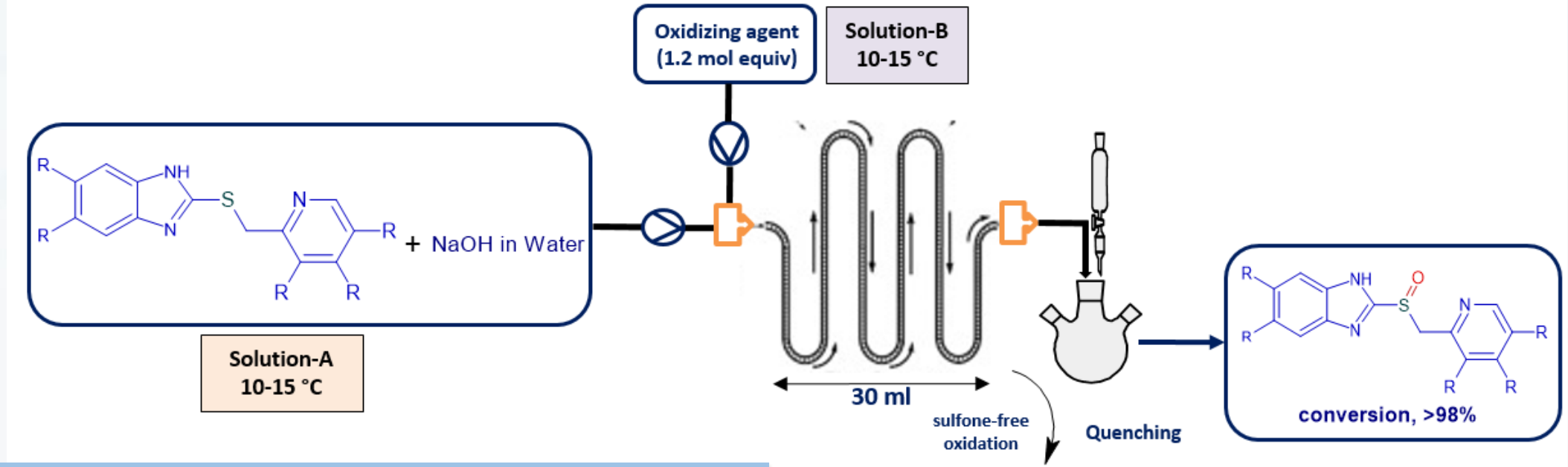
Amar-4P-100ML-SS316

Photo Flow Reactor

SUCCESSFUL FLOW CHEMISTRY REACTIONS



CASE STUDY-1: OXIDATION

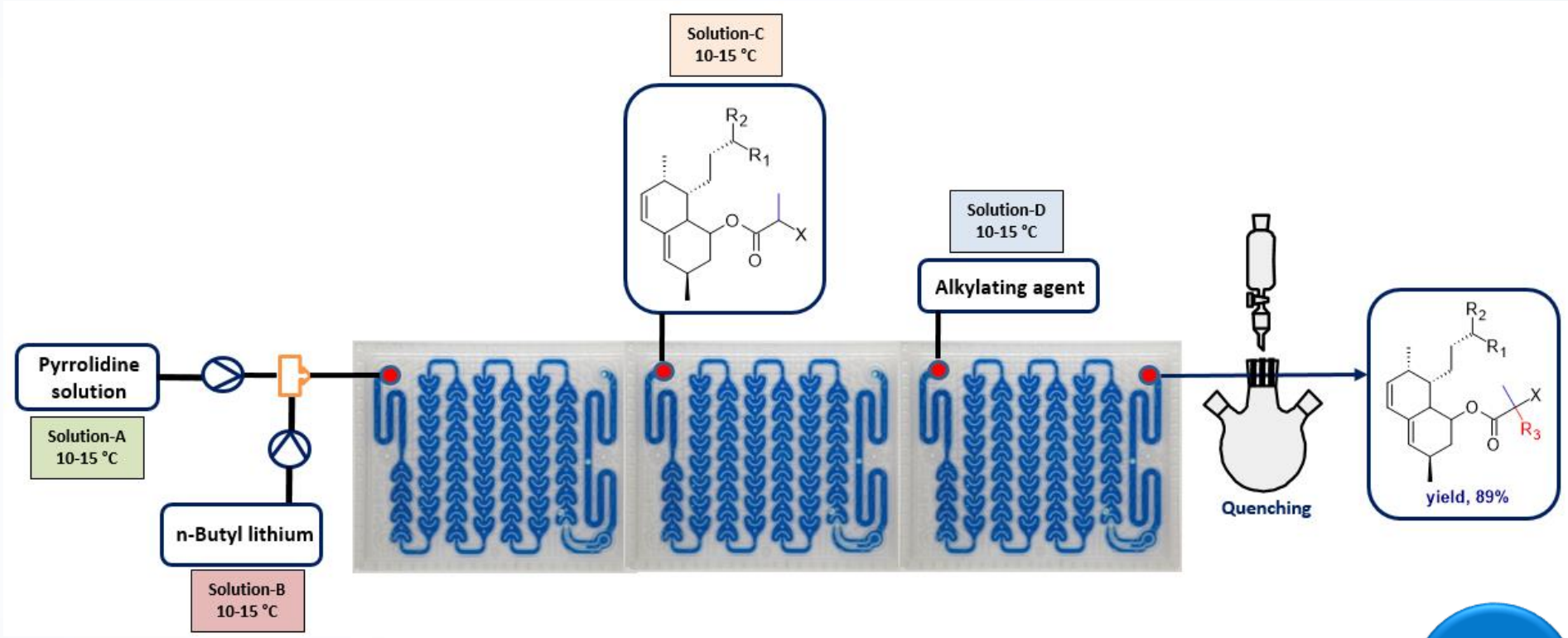


Advantages:

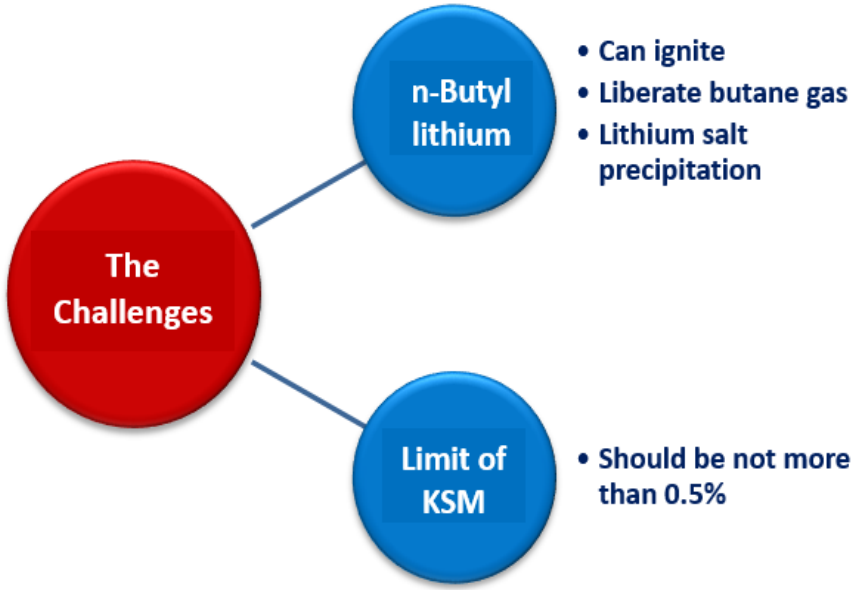
- Successfully converted from lab scale to plant scale (up to 500 Kg batch size)
- Regular production in plant using continuous mode
- Over-oxidation of sulfoxide to sulfone has been avoided in flow
- US & CEP filing has been approved for flow process
- Solvent consumption reduced by 60%
- HPLC purity achieved >99.5%
- Costing reduced to 50% in flow compared to batch
- Capacity increased from 5 T/month to 10 T/month

Plug Flow Reactor (Plant Set-up)

CASE STUDY-2: *n*-BUTYL LITHIUM REACTION – FLASH CHEMISTRY



Parameter	Batch process	Flow process
Reaction Temp	-75 to -70 °C	10 – 15 °C
Reaction time/Residence time	3-4 h	3 min
Product Conversion	82%	>95%
Solvent	Tetrahydrofuran (8 T)	Toluene (3 T)
Safety	Low	High



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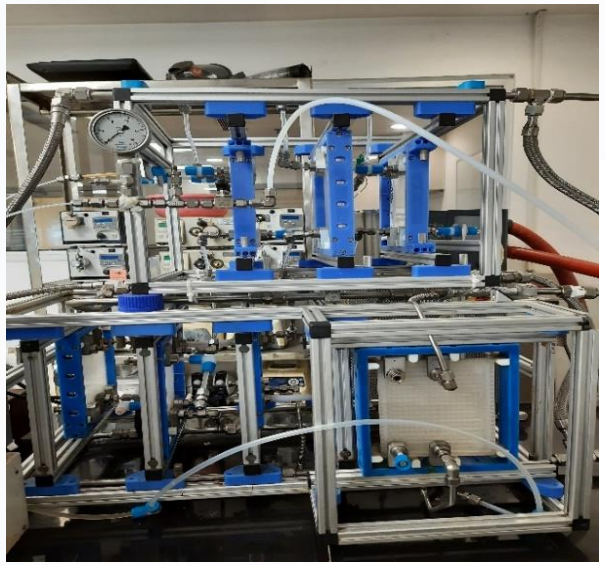


Corning G1 Reactor (Lab Set-up)

Seamless Scale-up from Gram to Tonnage Scale

55x times

Corning G4 Reactor (Plant Set-up)

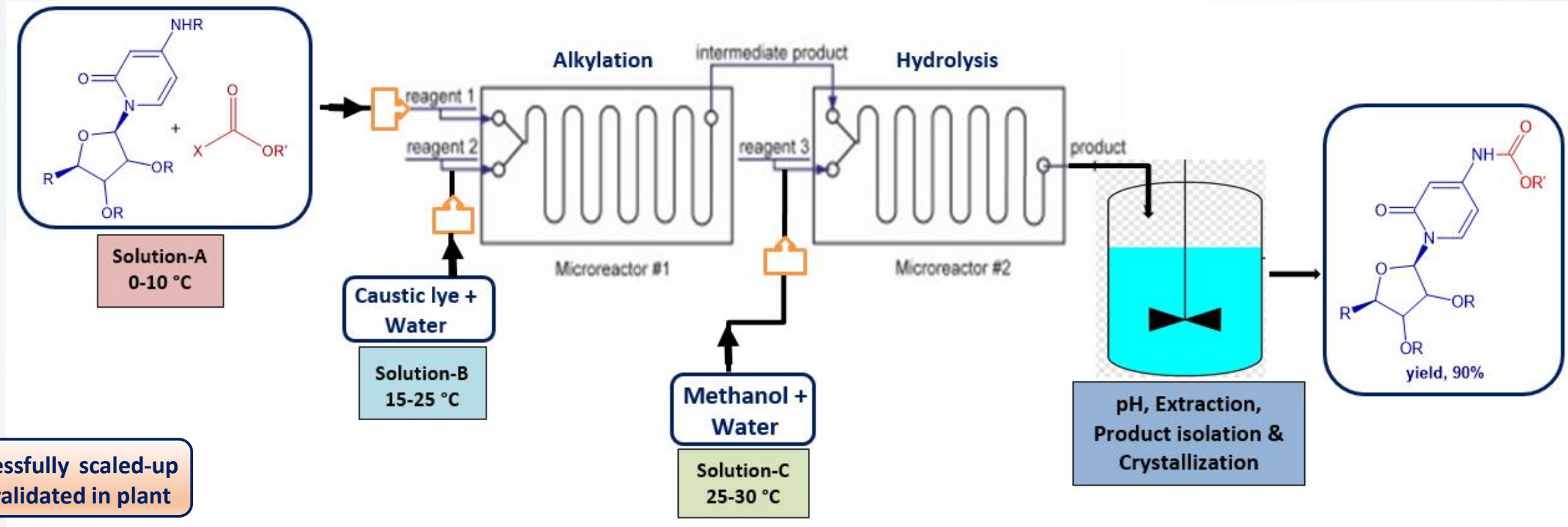
G1 Observations:

- Solidification observed in initial trials (precipitation of lithium salt)
- Over pressurization of system
- Cleaning of G1 reactor
- Start-up & Shut down procedure

G4 Observations/Challenges (Key take-away):

- Precipitation of lithium salt
  - ✓ *n*-Buli switched from 3.2 M to 1.6 M
- Auto-cleaning of G4 reactor
  - ✓ Cleaning of reactor with solvent at fixed time interval to avoid pressurization of system (Pressure raised from 10.5 Bar to 15.5 Bar)
- Precise temperature control of feed lines
  - ✓ to avoid exotherm

CASE STUDY-3: Alkylation and Hydrolysis (Telescoped Continuous Flow Synthesis)



Successfully scaled-up and validated in plant

Reaction parameters	Batch process	Flow process	Key achievements
Solvent:	DCM (22 T)/ Ethyl acetate (14 T)	DCM (9 T)/ Ethyl acetate (7 T)	Volumes of solvent get reduced to 50%
Yield:	70%	85%	High yield compared to batch
Process Time cycle: (Manufacturing)	17 days	8 days	~60% Process time cycle reduction

CASE STUDY-4: CONTINUOUS LIQUID-LIQUID EXTRACTION (LLE)

Scaling-up

CHALLENGE (BATCH PROCESS)

- Aqueous layer has residual impurity which needs to be removed using organic phase extraction
- Multiple extractions are required followed by water and brine washings
- Lengthy process leads to product degradation and yield loss
- Process cycle time: 48 h

CENTRIFUGAL EXTRACTION IN CONTINUOUS MODE

- Complete extraction of product in organic layer in just single extraction, because of high mass transfer rate in centrifugal LLE.
- Less time of exposure, leads to less degradation
- Process cycle time: 8 h

ICH Q13: CONTINUOUS MANUFACURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Final version

Adopted on 16 November 2022

ICH Q13: CONTINUOUS MANUFACURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

OBJECTIVES

- Describe scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of continuous manufacturing.
- Provides clarification on the concepts of continuous manufacturing.

SCOPE

- Applies to the CM of drug substances and drug products for chemical entities and therapeutic proteins
- Applicable to the CM of new drugs, generic drugs, biosimilars and the conversion of batch manufacturing to continuous manufacturing for existing products.

In this guideline, the prerequisites of the main aspects of FDA and other regulation expectations, GMP and key aspects for successful CM are provided with the premise that the output materials from the BM and CM processes should have comparable quality.

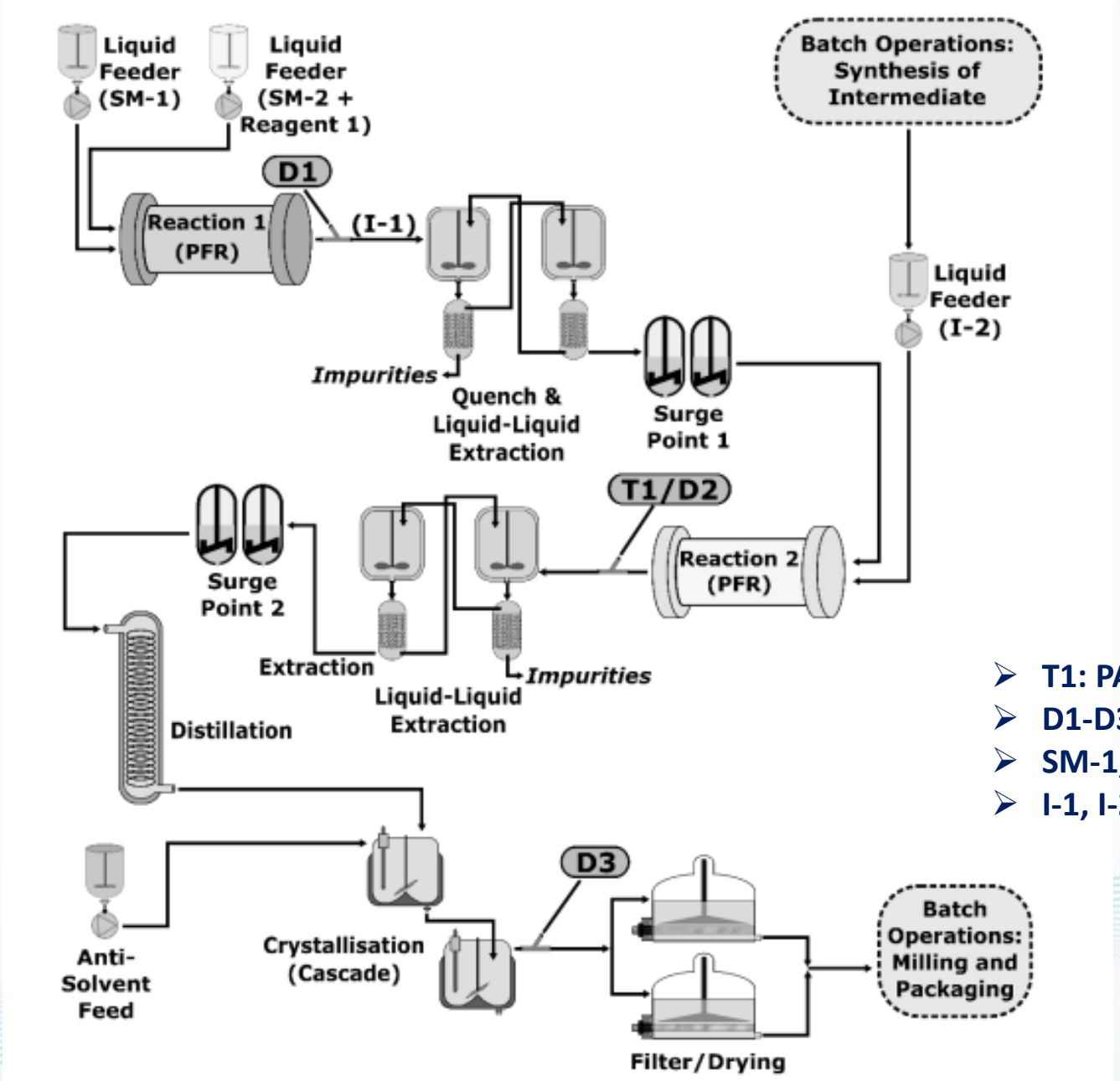
REGULATORY CONSIDERATIONS: ICH Q13

FOCUS AREA	Key aspects for submission of the Common Technical Document (CTD)
Description of manufacturing process and process controls	• Process flow diagrams of flow reactor system • A summary of start-up, shutdown, pause and restart procedures • Strategy for material diversion and collection • Process parameters (e.g., mass flow rate(s), temperature, pressure, residence time) • Critical aspects of selected equipment design and configuration
Control strategy	➢ Must ensure that output materials made over time are of the desired quality Must consider: • Input material attributes • Process monitoring and controls (sampling strategy and frequency) • PAT measurement frequency to the RTD (residence time distribution)
Batch description and batch size	➢ Size of a batch produced by CM can be defined in terms of: • Quantity of output material • Quantity of input material • Run time at a defined mass flow rate

cont....REGULATORY CONSIDERATIONS: ICH Q13

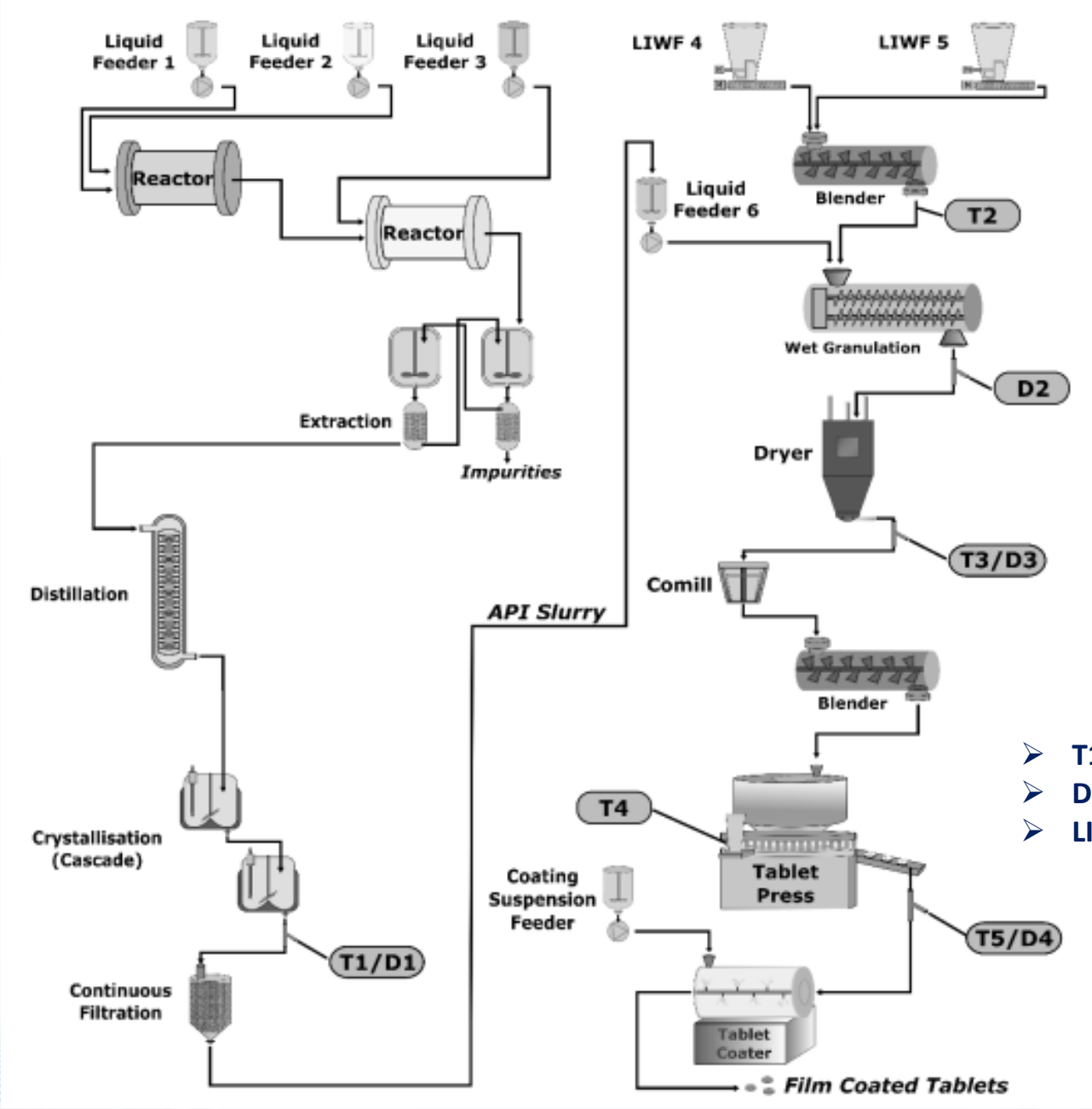
FOCUS AREA	Key aspects for submission of the Common Technical Document (CTD)
Drug substance and drug product stability	➢ No difference between CM and batch manufacturing modes for the regulatory expectations for stability data package
Conversion of batch process to CM	➢ Considering appropriate control strategy, BM process can be converted into CM process provided the output materials from the BM and CM process should have comparable quality
Process validation	➢ Requirements for process validation are similar for CM and BM process and also can follow the same standard approach of a fixed number of validation batches
Pharmaceutical Quality System (PQS)	➢ Expectations for the PQS are the same for BM and CM process, following pertinent ICH guidelines

EXAMPLE OF A DRUG SUBSTANCE CM SYSTEM



- T1: PAT
- D1-D3: Diversion points
- SM-1, SM2: Starting materials 1 and 2
- I-1, I-2: Intermediates 1 and 2

EXAMPLE OF AN INTEGRATED DRUG SUBSTANCE AND DRUG PRODUCT CM SYSTEM



- T1-T5: PAT and at-line test locations
- D1-D4: Diversion points
- LIWF4 and LIWF5: Loss-in weight feeders

BENEFITS ACHIEVED WITH FLOW TECHNOLOGY

PARAMETERS	BM PROCESS	CM PROCESS
Product selectivity	Low	High
Product conversion	Limited	Can be maximum
Reagent and Solvent	In excess	Very less
Infrastructure	Huge	Compact
Quality failure	Chances are there	Negligible, once process is optimized
Scale-up	Challenging	Seamless
CAPEX and OPEX	Relatively huge	Relatively 40% less
Production capacity	Limited by reactor size and infrastructure	Easy to increase with the existing set-up
Safety	Less safe	Completely safe

IMPACT OF CONTINUOUS FLOW MANUFACTURING ON BUSINESS

- Overall API cost reduction by improvement in yield and reduction in the quantities of reagents & solvents
- Less outsourcing of the products since exothermic and hazardous reactions can also be handled in-house safely
- Increased production capacity with safe operations
- Consistent batches with negligible failure
- Quick scale-up without failure
- Less infrastructure requirement
- Timely product delivery

EXPECTATIONS IN THE FUTURE

- Continuous manufacturing has the same regulatory requirements that batched size manufacturing processes.
- CM can potentially be a standard of drug manufacturing in the pharmaceutical industry.
  - ✓ Many regulatory agencies, including US FDA, EMA and PMDA, strongly support the implementation of CM technology.
  - ✓ CM is the necessary technology to realize Industry 4.0.
  - ✓ CM can innovate the manufacturing and improve the access to medicines.

CM will be a benefit for everyone.

Thanks