CCID, the UL/SSPC Lilly Pfizer Partnership

PARTNERSHIP STRUCTURE:

This partnership alliance was an Enterprise Ireland Innovation Partnership Project between **Pfizer** (with team members based in Ringaskiddy, Cork, ***Ireland***, Groton, Connecticut, ***US*** and *Singapore*), **Eli Lilly** (with team members based in Kinsale, Cork, ***Ireland,*** and Indianapolis, ***US***) and the SSPC Research Centre at the **University of Limerick** with the key objective of developing flexible platforms for **C**ontinuous **C**rystallization, **I**solation and **D**rying (**CCID**) from existing off the shelf technology for real-world active pharmaceutical ingredients (APIs).

The University of Limerick (UL) has established itself as a national nucleus for applied pharmaceutical research over the last decade and is currently home to SSPC, the SFI Research Centre for Pharmaceuticals. SSPC is a unique collaboration between academia and industry in the Pharma sector with the common goal of conducting world class applied pharmaceutical research, and in doing so train the next generation of scientists and engineers to meet the growing needs of the Pharma sector globally. Specifically relevant to this CCID project was the extensive engineering expertise available within UL, covering a wide range from fundamental crystallization research, physical property characterization, process development, application of process technology and process modelling.

Pfizer is one of Ireland's leading employers and the largest pharmaceutical sector investor and employer. One of the first pharmaceutical companies to locate in Ireland (1969), Pfizer has a rich heritage of innovation and expansion; this year marks the 50th anniversary of Pfizer establishing a manufacturing base in Ireland. Pfizer has over 3,300 colleagues across 6 locations based in Cork, Dublin, and Kildare. Total capital investment by the company in Ireland exceeds $7billion. Many of Pfizer's leading and newest medicines are manufactured for global export from Irish sites.

Lilly has been in Ireland since 1978 and today employs over 1,300 people. The manufacturing campus in Kinsale employs over 700 people, and uses complex chemical synthesis & biotechnology manufacturing processes to make active ingredients for medicines across therapeutic areas such as oncology, immunology and diabetes. The site is also involved in process development and optimization across both manufacturing platforms.

The highlight of the CCID partnership was the development of a continuous crystallization process for a Pfizer API, using an Eli-Lilly lab scale 2-pot MSMPR crystallization rig, and subsequent scale up of the crystallization to 2 20 L crystallizers and isolation on a high frequency filter (HFF) in the Pfizer KTL facility in Ringaskiddy, with a successful 95 hour continuous crystallization run.

Partnership Strategy:

Continuous manufacturing is a novel concept to the Pharmaceutical Industry. There is currently no end-end continuous crystallization, isolation and drying pharmaceutical process in operation at a commercial scale (figure 1). Pfizer, Ringaskiddy, Co. Cork, and Eli Lilly, Kinsale, Co. Cork, united with the common goal of identifying a solution to this problem, both providing €50,000

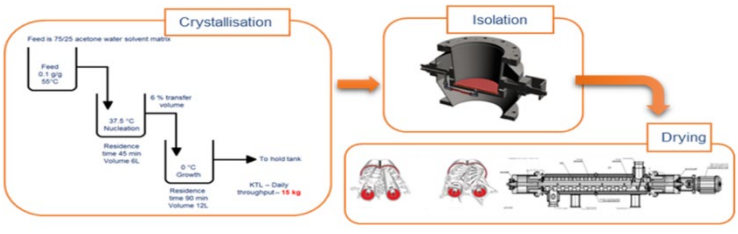

Figure 1: End to End Continuous Crystallization, Isolation and Drying

cash and €40,000 in-kind contribution to leverage an additional €250,000 from Enterprise Ireland via the UL based research lead, Dr Denise Croker.
CCID was a hugely successful partnership project. All activities took place with the full involvement of company and academic team members. Initial activities focused on defining the selection criteria for the API system, the crystallization unit, the isolation technology and the drying technology. This placed the UL researchers routinely at the company's sites. Once the equipment was in place (Eli-Lilly donated a lab scale 2-pot MSMPR to UL, Pfizer donated API material and a lab scale isolation unit) experimental testing of the unit operations took place at the University. The US Research and Development Centres of both companies also supported the project and participated in meetings throughout the duration of the project. Company team members provided input to the experimental testing, the UL researchers presented regular progress up-dates at monthly technical meetings via video conferencing allowing the US and Singapore based researchers of both companies to participate.

The UL researchers also regularly visited the Irish sites for technical meetings. A Lilly engineer and technician supported equipment installation locally at the UL laboratories. The two full-time UL researchers and a Pfizer Ireland colleague travelled to the US for face-to-face meetings with partners in the US sites in Indianapolis and Groton. They visited vendors with the US based Pfizer scientists. The US based Pfizer scientists also visited the Lilly site in Indianapolis for face to face meetings and site tours with scientists working at the cutting edge of continuous API manufacturing.

A BRITEST evaluation toolkit was used to develop selection criteria for the identified technologies and to rate all technology with the final result that the High frequency filter from Pfizer and a dryer from an external vendor was selected as optimum technologies for isolation and drying respectively. All members from UL and Industry sites (US and Irish) participated in this activity.

Dr Barbara Wood at UL completed all crystallization project work. A crystallization process modelling exercise was also completed with the aim of comparing the capabilities of available software packages namely, Dynochem (B. Wood), Matlab (R. Tyrell, via SSPC) and gCrystal (C.Polster, Lilly) to describe and predict the continuous crystallization of the Pfizer API using experimental input generated from batch crystallization at 1 L scale in Pfizer Process Development Labs located in Cork.

The UL crystallisation process was successfully scaled up at the Kilo Technology Laboratory (KTL, Cork) in Pfizer by Pfizer technical staff following a technology handover (figure 2). The UL researchers supported the demonstrations and Eli Lilly researchers were also in attendance, this in itself is a first for Irish academia and testament to the potential value realized in this work. The KTL also successful demonstrated the continuous isolation of API by integrating the high frequency filter to the continuous crystalliser, generating 10kg of API per 24-hour period.

CCID also leverage existing administration support structures within the SSPC, existing as an SSPC – associated project, and took advantage of existing SSPC procedures in relation to industrial interactions, Intellectual Property Management and Heads of Agreement.

The global project team consisted of:

UL:	**Denise Croker,** Barbara Wood, Christian Bouani/Jude Ngadaoyne, Rory Tyrell, Gavin Walker, Kieran Hodnett, David Egan.
Pfizer:	**Liam Tully,** Patrick Sweeney, Edel Hughes, Kevin Girard, David Pfisterer, David Walker, Pushkar Pendse Vincent Irwin.
Eli-Lilly:	**Stephen Jeffery,** Ciara Hood, Melba Simon, Ed Conder, Chris Polster

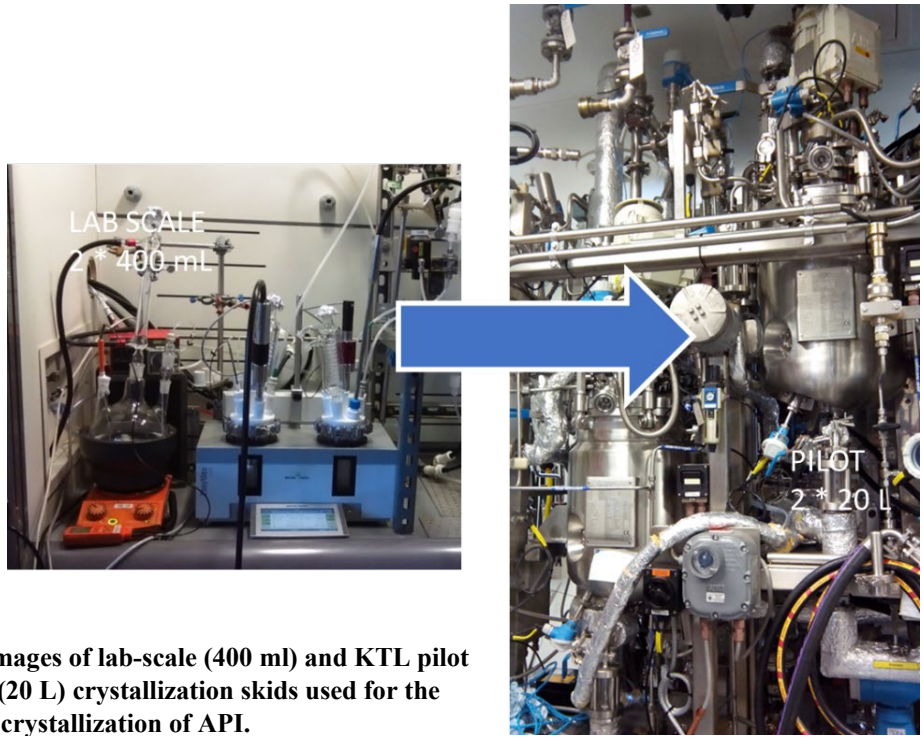

Figure 2: Images of lab-scale (400 ml) and KTL pilot plant scale (20 L) crystallization skids used for the continuous crystallization of API.

RATIONALE:

Continuous pharmaceutical manufacturing is expected to be adopted widely within the Pharmaceutical Industry to improve manufacturing efficiencies over traditional batch manufacturing, the benefits include the ability to deliver improved API consistency and robustness (Particle Size Distribution, morphology, flowability), lower capital costs, portable equipment, enabling of "Just In Time" manufacturing, continuous quality verification if desired and a key enabler of allowing the same equipment to be utilized in development and commercial manufacturing particularly at the scale of 500-5000 kg/yr.

Currently a lack of manufacturing equipment at the smaller pharmaceutical operating scale is limiting the realization of continuous pharmaceutical manufacturing especially at the crystallization, isolation and drying phase. Companies operating in the area typically revert to batch unit operations at this phase of the project. Continuous Crystallization, Isolation and Drying (CCID) is a vital step on the journey to fully integrated continuous pharmaceutical processing which will revolutionize pharmaceutical manufacturing. The goal of the CCID project was to develop an integrated processing platform for continuous crystallization, isolation and drying (CCID) of pharmaceutical process streams. The project also addressed the knowledge gap between existing (large-scale batch mode) pharmaceutical equipment infrastructure and future continuous equipment requirements, and in doing so broadened the capability and value of the Pfizer and Eli Lilly Irish manufacturing bases.

The CCID partnership significantly enhanced the in-house expertise in continuous downstream processing in Pfizer and Eli-Lilly. The skill-set developed in continuous manufacturing within Pfizer and Eli Lilly will differentiate the Irish manufacturing base within the respective company parent networks. Since commencing this partnership project both Irish manufacturing bases have received significant investment from their US based parent company for continuous process development, and capital investment in continuous manufacturing. Lilly and Pfizer locally continue to consult with each other on new developments in this technology space. Continuous isolation and drying will continue to be investigated by SSPC as the centre enters phase II of its funding period (2019 – 2025).

"For Pfizer, two results were achieved with this project, one been the successful running of the crystallisation and isolation for a full working week, and secondly the partnerships and relationships forged within Pfizer Cork, Singapore and US and also between Lilly Cork, Lilly US and UL, without them we wouldn't have achieved the milestones of the project".
Pat Sweeney, Pfizer KTL CCID Project Lead.

"The CCID project provided real insight into the operational challenges associated with transferring and academic solution into the industrial environment. Knowledge exchange between the academic an industrial project team was core to delivering the optimum solution. The project provided core industrial skills to 3 post doctorate researchers and was presented internationally in the UK and US".
Dr Denise Croker, CCID Project Lead and SSPC Executive Director.

INNOVATION:
Innovation was demonstrated throughout the partnership resulting in the development of a continuous crystallization process for a Pfizer API using a lab scale 2-pot crystallization rig at the Bernal Institute in UL as well as collaborative modelling work of the system. The successful subsequent scale up of the crystallization to 2 x 20 L crystallizers as well as isolation on the high frequency filter (HFF) in the Kilo technology Lab with a successful 95 hour process run before orderly shutdown with a yield improvement on the batch process from 85% to 89%. This crystallization process had considerable challenges around form control and crystallization kinetics when compared with a well characterized model API. Through this alliance, innovative solutions were demonstrated for designing a transfer system between the 2 crystallizers and also in the reduction of fouling with the crystallizers. The partnership project also identified and successfully trialed a unique double auger drying unit, commercially available, demonstrated drying capability to tight specifications with short residence time using continuous feed of wet API cake generated in the KTL.

The integration of the HFF unit to the KTL demonstrated the team work and innovative requirements of the project. The HFF (new prototype unit) was developed in Pfizer Groton and successfully integrated into the KTL using a multi-disciplinary team on the RNG site with support from UL researchers who performed characterization work of the filtration and modelled filtration timing and throughputs. The team had to innovate to ensure its successful integration utilizing existing infrastructure within the KTL. This Platform technology is now available to the manufacturing bases within Pfizer and Lilly for integration into continuous manufacturing.

OUTCOMES:
To date considerable outcomes have resulted from the partnership with further publications to follow. These provide a significant contribution to the body of knowledge on continuous API processing for the scientific community as a whole.

Project output Technical Report: CCID Final Report – executive summary and final project outputs, D. Croker, October 2017.

Publications:	Dynochem Webinars:
"Progress to date in the design and operation of continuous crystallization processes for pharmaceutical applications", B. Wood, K. P. Girard, C. S. Polster, D. M. Croker, *Org. Process Res. Dev., 2019, 23 (2), pp 122–144*	• May 2017: *"Utilizing DynoChem Modelling to Design the Continuous Crystallization of an Active Pharmaceutical Ingredient"* • Sept 2018: *"Utilizing DynoChem Modelling to Design the Continuous Crystallization of an Active Pharmaceutical Ingredient: Part II"*
Conferences:	**Additional/Associated Funding:**
• Academic and industrial partners invited to present at the **Royal Society of Chemistry/SCI- Continuous Flow Technology IV conference**. 14-16 May 2019 **Title: "***Continuous Crystallization of an active pharmaceutical ingredient: from Lab to Pilot Plant"* Barbara Wood, Pat Sweeney • **British and Irish Association of Crystal Growth Conference 2017** 27th - 30th June 2017 **Title:** *"Converting a Batch API Crystallization to a Continuous Crystallization with Scale up to the Pilot Plant"* Barbara Wood, Jude Ngadaonye, Kieran Hodnett, Denise Croker • **CM2017 Workshop: Adopting Continuous Manufacturing: Defining the Platform for Success** 22nd - 23rd Feb 2017 **Title:** *"Defining a Design Methodology for Conversion of a Batch API Crystallization to a Continuous Crystallization*" Kieran Hodnett, Barbara Wood, Jude Ngadaonye, Denise Croker • **AIChE Annual meeting San Franciso**, CA. 15 November 2016 **Title:** "*Defining a Design Methodology for Conversion of a Batch API Crystallization to a Continuous Crystallization"* Barbara Wood, Denise Croker, Kieran Hodnett	• *SFI Research Centres Infrastructure Award 2015: Crystallization, Isolation & Drying Technology Test Bed (CIDT2). €4M – D. Croker/SSPC* • *EI Feasibility Study Award 2017: Assessment of market potential for a continuous filtration and drying device for pharmaceutical applications. €14.5K – D. Croker/PMTC.* • *Inward investment in continuous processing development and continuous manufacturing capital investments at the Irish manufacturing bases.*

SOCIETAL AND COMMERCIAL IMPACT:

Robustness: The steady state operation achieved during continuous processing of API reduces variability and improves consistency through tighter control of product attributes, resulting in improved drug product manufacturing processing and fewer product losses.

Enabling Technology: Both Pfizer and Eli Lilly have proven expertise in developing continuous chemistry operations and bringing them to GMP (good manufacturing practice) manufacturing. The CCID project has the potential to provide a technical solution to 'back-end' processes of crystallisation, isolation and drying, thereby enabling fully integrated continuous processing. This integrated approach would strengthen the position of Eli Lilly Kinsale and Pfizer Ringaskiddy for the supply of clinical and commercial supplies of a range of new small volume API products within their organizations. Changes in the typical pharmaceutical API portfolio to smaller volume API volumes are driving manufacturing changes. With New Product API forecasts at 500–5,000 kg/yr vs. 20,000 400,000 kg/yr there is a requirement for smaller scale equipment options so that batch size is not too large for these high value products (i.e. there is significant risk with a high inventory of high value API).

Technology Transfer: The technology developed within this programme will reduce the risk of scale up of processes for Eli-Lilly and Pfizer and will offer the benefit of a faster, more robust technology transfer. With smaller equipment footprints, technology transfer can be achieved by simply relocating/reproducing the operating equipment to/at the manufacturing site.

Competitiveness: Continuous manufacture offers potential benefits in quality, robustness, safety and lower capital expenditure. These benefits will drive an increase in competitiveness. As detailed above, the change in the pharmaceutical API portfolio towards smaller volume products means that a change in manufacturing is required for Eli Lilly and Pfizer to remain competitive. Multiple small scale batch processing units can be very inefficient especially if used for short campaigns of multiple products with complex, time-consuming

changeover cleaning requirements. Dedicated continuous processing equipment is an attractive option which will be enabled through programmes such as CCID.

Societal Impact: In the course of this project all UL based research staff participated in the SSPC Public Engagement programme, which extended the reach of this research outside the research community. School visits, lectures to general audiences and interaction with school teachers forms part of this program to inform and educate society as to the impact of research conducted in Ireland. Specific to CCID, this would involve explaining the rationale behind continuous crystallization and operations to a lay audience and highlighting some of the research being conducted within the project.