SSPC

The SFI Research Centre for Pharmaceuticals

A World Leading SFI Research Centre

Science Foundation Ireland sfi For what's next

INDUSTRY CASE STUDIES

HOST INSTITUTION

UNIVERSITY OF LIMERICK OLLSCOIL LUIMNIGH

PARTNER INSTITUTIONS

DCU Dublin City University

Maynooth University National University of Ireland Maynooth

NUI Galway OÉ Gaillimh

RCSI

Trinity College Dublin Coláiste na Tríonóide, Baile Átha Cliath The University of Dublin

UCC University College Cork, Ireland Coláiste na hOllscoile Corcaigh

UCD University College Dublin An Coláiste Ollscoile, Baile Átha Cliath

Waterford Institute of Technology

Scale-Up the collaborative project

Scale-up Systems develops the world's leading drug substance process development software for scientists and engineers in the Pharmaceutical industry.

LEAD RESEARCHERS

Prof. Harry Van den Akker and Dr Javad Zeinali at the University of Limerick.

THE PURPOSE OF THE PROJECT

To investigate the hydrodynamics of commonly used lab-scale reactor systems under typical operating conditions. Predictions of mixing using traditional chemical engineering relationships become more difficult as the scale of operation decreases below a few litres. This project completed a number of computational fluid dynamic simulations allowing more detailed process characterization and will enable users of the company's Dynochem software to make more accurate predictions when scaling-up or down as part of pharmaceutical development and manufacturing.

EXPERTISE

The Van den Akker group brought expertise in CFD modelling and fluid mechanics and Scale-up Systems brought know-how of reactor vessels, including dimensions, suitable operating conditions and general behaviour as calculated using chemical engineering principles; prior knowledge of CFD and some input files for OpenFoam® software.

THE RESULTS

The output of this project has been the advancement of knowledge of small-scale chemical reactors in order to better understand mixing performance at these scales and to translate that to larger scale equipment.

This new level of understanding can potentially improve efficiencies in drug substance production within the pharmaceutical sector, especially the reduction of batch failures and increased right first time performance.

A licence to the project technology was granted to Scale-up Systems in 2020. A further collaborative research project was undertaken in October 2020. The outputs of this second project were the subject of another licence to Scale-up Systems in early 2021.

Scale-up Systems will use the simulations developed to provide users of their Dynochem software with more accurate predictions of the scalability of processes in early-stage development.

"It was a pleasure for our team (Dr Andrew Bird and Dr Charles Gordon) to work with the Van den Akker modelling group in SSPC with support from Aisling Arthur and the University of Limerick Technical Transfer Office. The work was conducted to the highest academic and professional standards and provides reassurance about scale-up from these very common lab set-ups.The approach of the modeling team made excellent use of state of the art facilities and automation opportunities as well as their knowledge of fluid mechanics and modeling techniques". **Joe Hannon, CEO Scale-up Systems**

"It was a pleasure working with Scale-up Systems as it also allowed us to perform simulations of varying levels of sophistication for geometries and conditions relevant to industry and to check their mutual deviations and their respective pros and cons. The response and input from Scale-up Systems was to the point and valuable. The support by TTO was very appropriate and welcome." **Prof. Harry Van Den Akker**

MOMEnTUM Project:

A Modelling approach to Design Predict and Control manufacturing processes

THE CHALLENGE

The Manufacture of pharmaceutics, biopharmaceutics and chemical products is complex and costly. Predictive modelling of process change helps to reduce waste and down time. In drug product manufacturing, most models used for the prediction of direct compression (DC) and roller compaction (RC) processes are process-parameters-based; meaning that the models do not consider the material characteristics. The variability in the same equipment and different equipment size and brand has an impact on the ability to process and transferability of complex blends and models. Another technology used in drug product manufacturing is Spray Drying (SD) however, the handling and processing of large molecule APIs at elevated temperature is uncommon and challenging. The Johnson & Johnson Automation Centre of Excellence (ACoE), presented a challenge to the SSPC to develop a modelling approach that would minimize manufacturing cycle time and develop cost effective, optimized processes for the manufacture of pharmaceuticals and biopharmaceuticals

THE SOLUTION

SSPC researchers combined existing theoretical approaches with a Design of Experiment (DoE) approach to develop 3 models that consider the physiochemical properties of excipients and APIs:

1. **A Continuous Manufacturing tablet compression integrated work stream** that allows J&J to predict compression behaviour from powder properties as well as convert between operating conditions of one press to another was developed. This required extensive characterization of a wide range of materials, across a range of equipment. The goal here was to build on existing modelling approaches to enable prediction of tablet critical quality attributes, tablet press performance and control settings enabling faster tech transfer to other lines or evaluation of new product powder properties as suitable candidates for Continuous Manufacturing.
2. **A Continuous Manufacturing Roller compaction work stream** to assess roller compaction behaviour of specific blends to J&J was developed. The modelling approach developed has been integrated into the J&J modelling library and is helping to inform J&J with respect to standards, technology transfer and equipment selection. These models are contributing to the reduction of technology transfer timeline and cost associated with Design of Experiments.
3. **A predictive model for the Spray Drying of Biopharamceuticals** was developed. SSPC researchers developed a spray drying modelling approach for removing moisture and compared this approach to the more commonly used freeze drying approach. Spray drying is an alternative technique to freeze drying that provides lower operation costs, continuously and with higher efficiency.

THE IMPACT

Participation in this project has benefited J&J through increased process understanding and ultimately leading to increased competitiveness by leveraging the diverse skillset and experience of the SSPC team.

"As we improve our understanding of the science and engineering in the development of emerging technologies, the SSPC collaboration with J&J allows us to better serve our customers and patients. This project supports our future growth by allowing a more efficient evaluation of the transformation of batch-mode processes to continuous manufacturing- mode one, which in turn enables production cycle time reductions, reduction of risk of rejects, scrap and re-processing and promotes easier implementation of real time release."
Jorge Belen, Scientific Fellow, Janssen Supply Chain Technical Operations, Johnson & Johnson.

De Souza Process - Pregabalin: Transformed Crystallization

A partnership between Pfizer (Ringaskiddy, Cork, Ireland) and SSPC, the SFI Research Centre at the University of Limerick.

THE CHALLENGE

In 2012, Dr. Patrick Frawley started taking Lyrica (Pregabalin) for severe nerve pain associated with his spine. He decided to use his expertise in predictive modelling, process design and fluid mechanics to reduce the cost of manufacture. The strong working relationship between Dr. Patrick Frawley, (UL) & Pfizer facilitated easy interaction and a SFI TIDA programme application was assembled. Two postdocs in UL worked with the Pfizer team in the Process Development Centre Cork, who shared manufacturing procedures and materials. The problem statement was clear and related to process inefficiency, complexity and cost.

THE SOLUTION

The finalised innovative solution developed was divided into two parts.

The first part of the solution involved changing from a complex four step crystallization procedure using a modified solvent matrix to a single cool down procedure. This provided considerable benefits, in terms of time, throughput, solvent costs and Particle Size Distribution. Despite the many benefits of this approach, application of this step alone had been calculated to result in a similar yield to the current crystallisation procedure at plant scale - hence the requirement for a further step.

The second part of the solution focused on maximising yield. It is critical to maximise yield as API which is not returned from the solution represents a loss, and this can be a significant expense for the pharmaceutical manufacturer. This was realised by pressure recrystallization thus increasing the solvent boiling point and allowing for a higher solubility at the process start. It is important to note that the improvements described could be applied either individually or synergistically in combination. A lack of uniformity in particle size distribution can have consequences for downstream processes such as filtering and drying. The pressurisation approach has the advantage of preserving the benefit of a monomodal PSD. Pressure recrystallisation, as a means of improving yield, has been championed in the University of Limerick using several commercially available API's including paracetamol. A novel test rig, developed in the University, allows for non-intrusive high temperature / high pressure measurements, which could not be obtained using the standard gravimetric approach. This platform technology is being developed further with potential commercialisation in the future. This approach is been considered for other processes being redesigned by the PDC at Pfizer.

THE IMPACT

The research has significantly impacted a manufacturing process within the pharmaceutical sector. This is evident through an increase in yield, improved efficiencies, and reduction in solvent use and complexity, improvements in throughput and better particle consistency. The candidate API selected for optimisation, Pregabalin known by the brand name Lyrica, was and remains one of Pfizer's biggest multi billion euro selling APIs. Significant economic benefits will be derived from this research. This work has also built bridges and credibility between Irish plants and US corporate units through active engagement, regular meetings with Research Laboratories in the US and the exchange of key staff. Publication: Solubility of (S)-3-(Aminomethyl)-5-Methylhexanoic Acid in Pure and Binary Solvent Mixtures, J. Chem. Eng. Data, DOI: 10.1021/acs.jced.5b00736.

"An application that has significantly impacted a manufacturing process within the pharmaceutical sector."
Prof Liam Tully, Pfizer Global Process Development Centre.

CCID, the UL/SSPC Lilly Pfizer Partnership

A partnership alliance with Enterprise Ireland Innovation Partnership Project between global teams at Pfizer (Ringaskiddy, Cork, Ireland, Groton, Connecticut, US and Singapore), Eli Lilly (Kinsale, Cork, Ireland, and Indianapolis, US) and SSPC, the SFI Research Centre at the University of Limerick.

THE CHALLENGE

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. Pfizer, Ringaskiddy, Co. Cork, and Eli Lilly, Kinsale, Co. Cork, united with the common goal of identifying a solution to this problem. Therefore, the key objective is developing flexible platforms for Continuous Crystallization, Isolation and Drying (CCID) from existing off the shelf technology for real-world active pharmaceutical ingredients (APIs).

THE SOLUTION

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.

THE IMPACT

The UL crystallisation process was successfully scaled up at the Kilo Technology Laboratory (KTL, Cork) in Pfizerby Pfizer technical staff following a technology handover. 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 industrialinteractions, Intellectual Property Management and Heads of Agreement.

The CCIDpartnership 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 through 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.

SSPC PhD industry placement programme: A case study with MSD

MSD, a current Tier 1 member of SSPC, the Science Foundation Ireland Research Centre for Pharmaceuticals have been partnering with SSPC since 2009 and through this partnership have advanced knowledge and 'know how' on site particularly in the area of Crystallisation. Membership with SSPC has helped to strengthen the Irish manufacturing operations as it positions itself to continue to move up the value chain and compete globally for R&D projects.

SSPC's success is defined through its unique collaboration abilities and building R&D excellence in one of Ireland's largest industries. The role that industry members play within the SSPC is a multi-faceted one that is successful in both responding current needs of the sector and anticipating the skills and training necessary to mentor future research leaders.

A key impact of SSPC is the creation of a unique talent pipeline with the transition rate of SSPC researchers to industry currently standing at 70%. One of the key drivers facilitating the high number of transitions to industry is the SSPC PhD industry placement programme, which brings students into the industrial environment for a three-month placement aligned with their research area. This exposes researchers to the realities of industrial processing while simultaneously providing industry with an insight into current research innovations.

MSD has hosted six SSPC PhD students to date and the placement programme has proven very beneficial to all parties facilitating knowledge exchange and upskilling between both student and staff. The exposure to cooperative mentoring by industrial members provides students with experience in project management, problem-solving and develops the skills needed to communicate research to various audiences. The supplementary training that SSPC students receive during their placements ensure that our graduates have industrially-relevant skills to support the pharmaceutical and biopharmaceutical industry.

The Student Placement Story

SSPC PhD student Barry Long, was placed at MSD Ballydine in 2019 and after his time in MSD his opinion on industry has completely changed. He looks forward to graduating next year and, hopefully, being able to return to industry.

Read about his experience:
"In 2017, MSD invested €40 million in a new spray drying facility at Ballydine. As my PhD involves spray drying, it was great to be able to work in a company that had recently invested in a spray dryer as I was able to learn at the perfect pace. Before my placement, I had some experience in a supplier quality and regulatory compliance role which made me think industry, consisted of paperwork only!

Themajority of my time at MSD was spent working on the spray dryer but I was lucky enough to have the opportunity to witness the other operations that took place on site, from API manufacture to tabletting to physical characterisation of materials. This provided me with a good idea of how life in the pharmaceutical industry typically goes from day to day. I was delighted that I was able to complete work that was relevant to my PhD as well as understand new processes, helping expand my experience.

The major differences I found between industry and academia involved the level of planning and understanding. Unlike academia, it is not possible to be able to decide what your plan is at the start of each day and, instead, weeks if not months of planning is required for each bit of work undertaken. The time I spent in MSD has completely changed my perspective and as I get closer to graduation, I look forward to making the move to industry and who knows maybe even back to MSD."

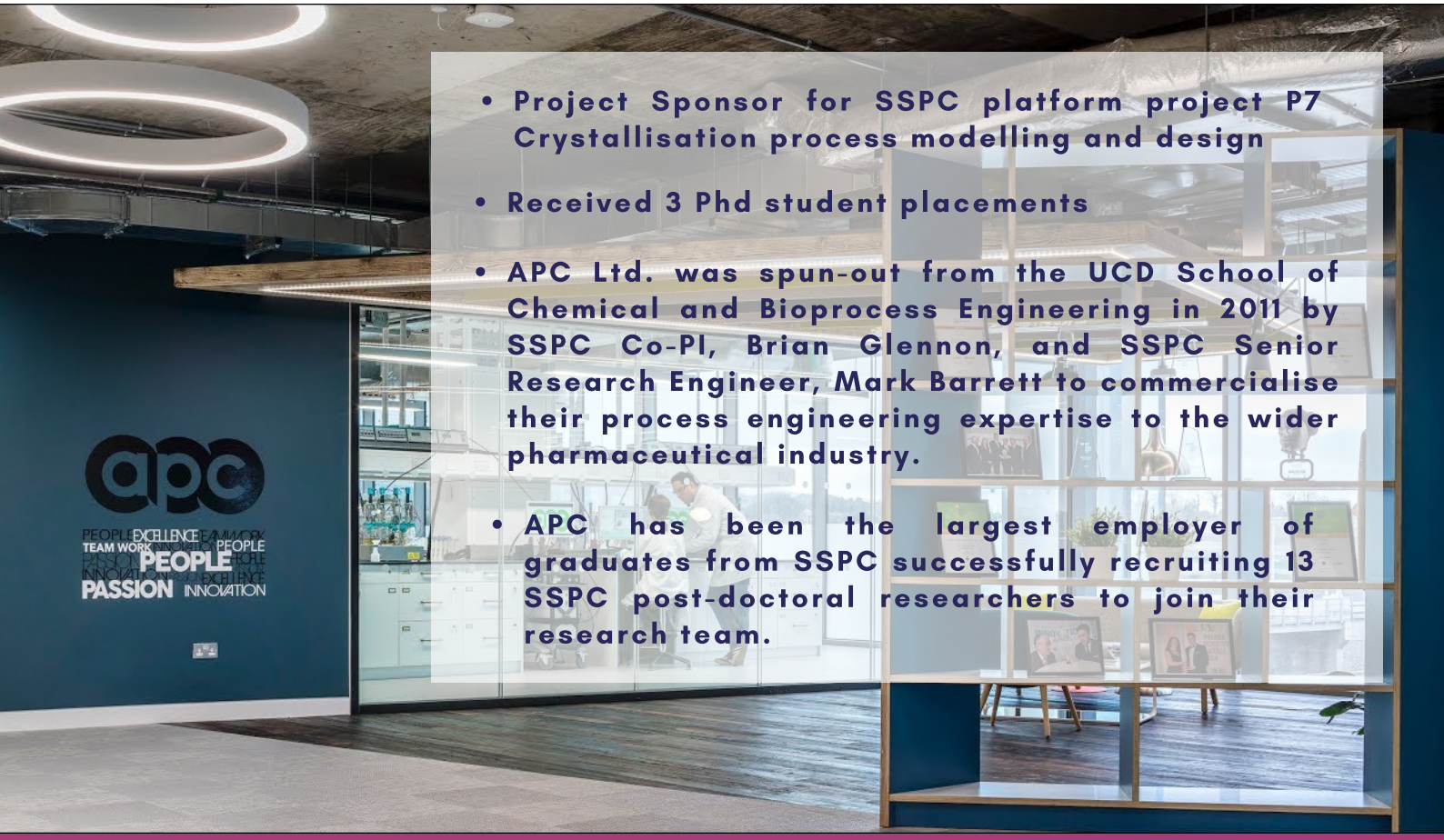
"MSD has hired a number of PhD graduates from SSPC and intends to hire more in the future. Many of the PhD students in the SSPC who have been exposed to the innovative and applied research projects with industry along with the new technologies at the SSPC are well positioned to take up these positions in companies like MSD."
Tom O'Ceallaigh, Director of Engineering, MSD

APC
Partnering with SSPC since 2013

Partners in Pharmaceutical Process Engineering

SSPC

APC brings together unique technology with a world class team of scientists and engineers, working across multiple therapeutic areas.



- **Project Sponsor for SSPC platform project P7 Crystallisation process modelling and design**
- **Received 3 Phd student placements**
- **APC Ltd. was spun-out from the UCD School of Chemical and Bioprocess Engineering in 2011 by SSPC Co-PI, Brian Glennon, and SSPC Senior Research Engineer, Mark Barrett to commercialise their process engineering expertise to the wider pharmaceutical industry.**
- **APC has been the largest employer of graduates from SSPC successfully recruiting 13 SSPC post-doctoral researchers to join their research team.**

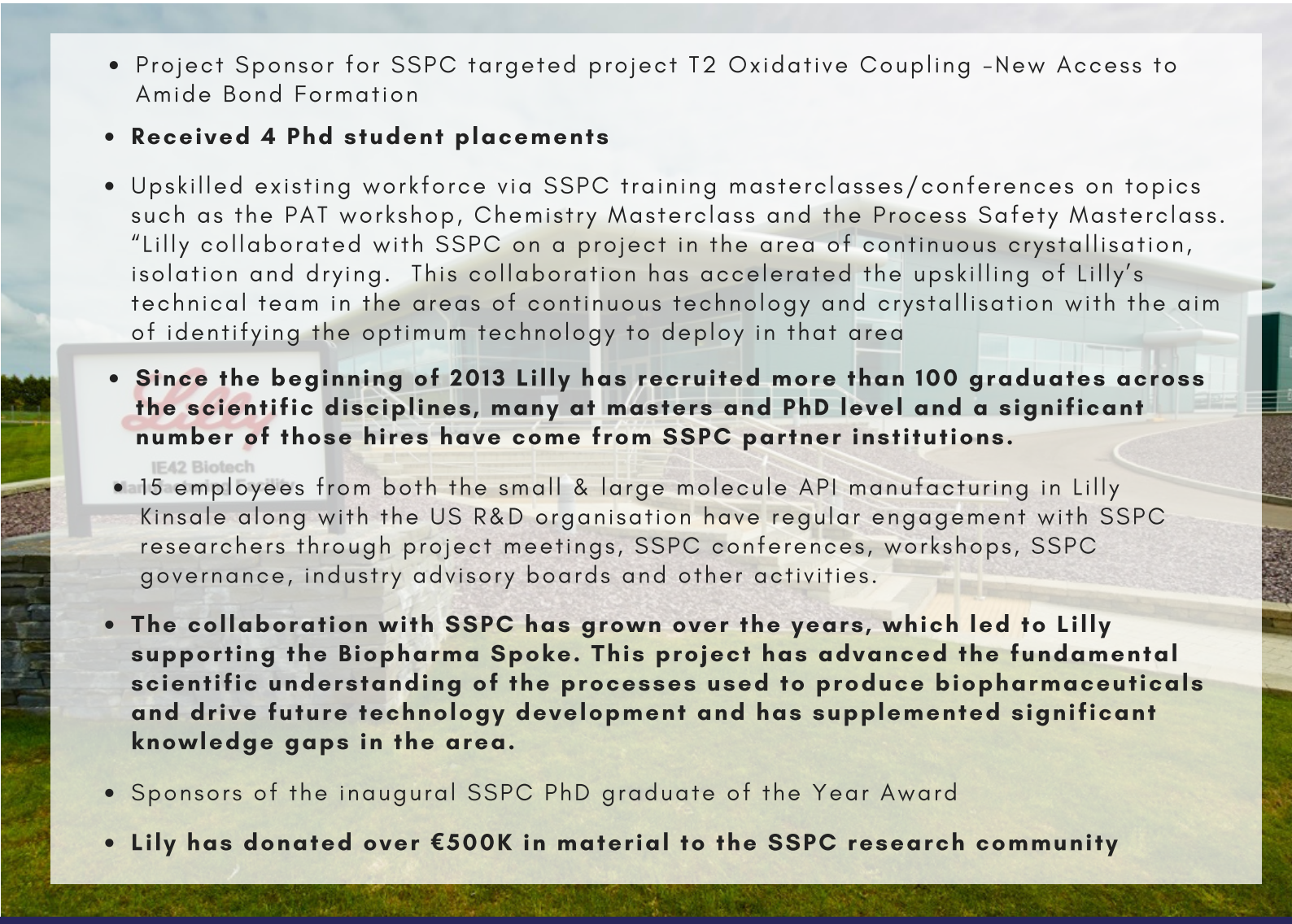
"Our support into the Centre research focus, educational development programs and talent development is simply essential to APC's future and sustained growth."

"The international standing and "brand awareness" of SSPC contributes greatly to the research excellence reputation of Ireland and our partnership with the Centre offers tangible benefits to the global profile that APC has built."

"A key aspect for APC in advancing our technology development and research capability is working with the brightest and best minds. It is the blend of innovative technology platforms and research prowess that enables APC to underpin the acceleration of new medicines to the market and more importantly, to the patient."
Mark Barrett, CEO & Co-Founder of APC

Eli Lilly: Partnering with SSPC since 2008

Lilly's Kinsale site has a reputation for technical excellence across both synthetic chemistry and biotechnology. They partner closely with Lilly's R&D division to bring the next generation of innovative medicines to patients around the world. Their work is technically demanding in a work environment that is dynamic and strongly team-based.



- Project Sponsor for SSPC targeted project T2 Oxidative Coupling -New Access to Amide Bond Formation
- **Received 4 Phd student placements**
- Upskilled existing workforce via SSPC training masterclasses/conferences on topics such as the PAT workshop, Chemistry Masterclass and the Process Safety Masterclass. "Lilly collaborated with SSPC on a project in the area of continuous crystallisation, isolation and drying. This collaboration has accelerated the upskilling of Lilly's technical team in the areas of continuous technology and crystallisation with the aim of identifying the optimum technology to deploy in that area
- **Since the beginning of 2013 Lilly has recruited more than 100 graduates across the scientific disciplines, many at masters and PhD level and a significant number of those hires have come from SSPC partner institutions.**
- 15 employees from both the small & large molecule API manufacturing in Lilly Kinsale along with the US R&D organisation have regular engagement with SSPC researchers through project meetings, SSPC conferences, workshops, SSPC governance, industry advisory boards and other activities.
- **The collaboration with SSPC has grown over the years, which led to Lilly supporting the Biopharma Spoke. This project has advanced the fundamental scientific understanding of the processes used to produce biopharmaceuticals and drive future technology development and has supplemented significant knowledge gaps in the area.**
- Sponsors of the inaugural SSPC PhD graduate of the Year Award
- **Lily has donated over €500K in material to the SSPC research community**

"The benefit of SSPC to the company is that it provides a 2-way mechanism of communication flow between the industry and academia in terms of current and future challenges for the industry and current and future research trends. This allows for development of innovative and productive methods of development and manufacture of future medicines cost effectively to the benefit of all involved and especially the patient. It also guarantees a pipeline of scientific talent going forward which is a key factor in the industry's current success and future growth in Ireland."

"Moving forward Eli Lilly Kinsale are excited to leverage the technical expertise within the SSPC to collaborate on this project. The development of new catalytic methodologies and application in the synthesis of existing and potentially new medicines will benefit patients around the world."

Humphrey Moynihan, Research Advisor, Technical Services/ Manufacturing Science Eli Lilly, Cork

Pfizer
Partnering with SSPC since 2009

Pfizer are committed to applying science and our global resources to bring therapies to people that improve health and well-being at every stage of life.

- **Project Sponsor of 5 research projects and has benefitted significantly from a steady stream of well-trained students and their placements**

- The PDC group collaborated with SSPC investigators to deliver an innovative improved manufacturing process for one of the company's world leading medicines. The work was subsequently repeated at laboratory and kilo Laboratory scale in Pfizer.

- **2 Joint Publications with SSPC:**

Progress to Date inthe Design and Operation of Continuous Crystallization Processes for Pharmaceutical Applications Barbara Wood, (SSPC) Kevin P. Girard (Pfizer Groton), Christopher S. Polster (Eli Lily Indiana), and Denise M. Croker (SSPC)

- **Application of New technology to a Mature Piroxicam Crystallisation Process to Gain Process Understanding and Control, via Industrial Academic Collaboration Anthony Maher (Pfizer Cork) Benjamin Kieran Hodnett (SSPC) Niall Coughlan (Pfizer Cork), Marie O'Brien (Pfizer Cork) and Denise Croker (SSPC).**

- The SSPC project in Continuous Crystallisation, Isolation and Drying (CCID) with Pfizer and Eli Lilly led by Dr Denise Croker, SSPC Executive Director, has accelerated the upskilling of the Pfizer in house technical team in the areas of continuous technology and crystallisation and experimental apparatus is being replicated at Pfizer and ultimately will form the cornerstone of a major change in the way Pfizer manufactures pharmaceuticals.

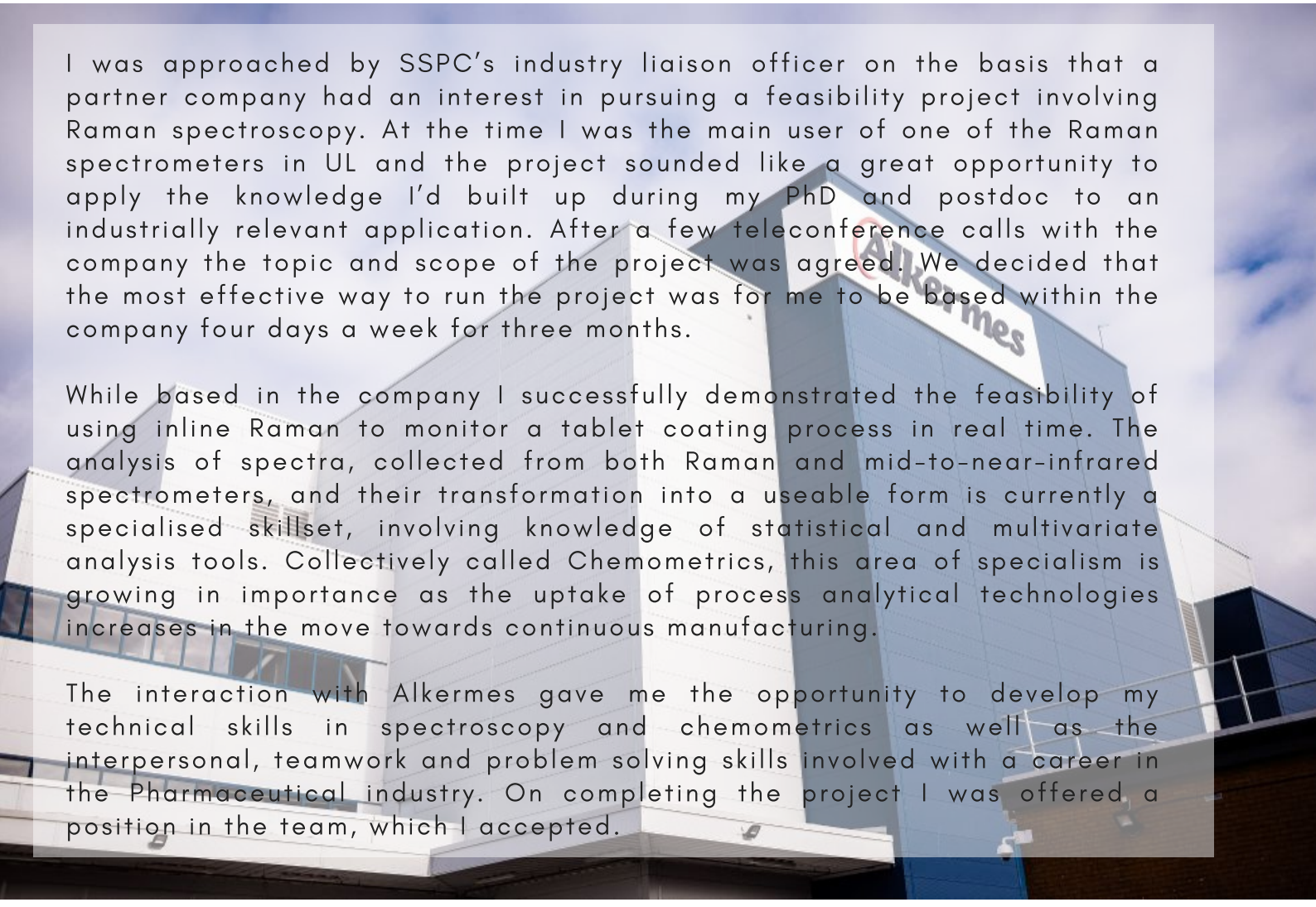
"Pfizer and its collaborators have hired several such students, and these students make an immediate impact in their roles in industry. We have hired two SSPC students specifically due to the expertise they developed in the centre."
Dr Kevin Girard, Associate Research Fellow, Pfizer, Groton, CT, USA.

"The SSPC construct provides a means for industry and academia to collaborate to address common industry needs, while allowing individual companies to carry out their own proprietary research. Through the SSPC, a community of skilled researchers are trained to address industrially relevant but proprietary processing issues. Access to high calibre researchers through the SSPC is of great benefit to Pfizer and has resulted in internal manufacturing process improvements. We look forward to further collaborations with the centre in the coming years."
Gerald Kierans, Technical Services Director, Pfizer, Grangecastle.

Alkermes - SSPC postdoctoral researcher placement

Alkermes plc is a fully integrated, global biopharmaceutical company developing innovative medicines for the treatment of central nervous system (CNS) diseases.

Catherine Potter
SSPC Postdoctoral Researcher, University of Limerick, now Scientist (Chemometrics), Alkermes



I was approached by SSPC's industry liaison officer on the basis that a partner company had an interest in pursuing a feasibility project involving Raman spectroscopy. At the time I was the main user of one of the Raman spectrometers in UL and the project sounded like a great opportunity to apply the knowledge I'd built up during my PhD and postdoc to an industrially relevant application. After a few teleconference calls with the company the topic and scope of the project was agreed. We decided that the most effective way to run the project was for me to be based within the company four days a week for three months.

While based in the company I successfully demonstrated the feasibility of using inline Raman to monitor a tablet coating process in real time. The analysis of spectra, collected from both Raman and mid-to-near-infrared spectrometers, and their transformation into a useable form is currently a specialised skillset, involving knowledge of statistical and multivariate analysis tools. Collectively called Chemometrics, this area of specialism is growing in importance as the uptake of process analytical technologies increases in the move towards continuous manufacturing.

The interaction with Alkermes gave me the opportunity to develop my technical skills in spectroscopy and chemometrics as well as the interpersonal, teamwork and problem solving skills involved with a career in the Pharmaceutical industry. On completing the project I was offered a position in the team, which I accepted.

"We were interested in introducing real-time spectroscopic analysis tools into our pipeline development activities with a focus on Raman analysis. Being able to temporarily bring an experienced SSPC postdoctoral researcher into the department provided us with an opportunity to achieve this goal. Cathy's previous experience with Raman spectroscopy and data analytics allowed her to deliver the project requirements, and identified additional areas of chemometric application for further development."

Alkermes