Institution: University of Bradford		
Unit of Assessment: B12 Engineering		
Title of case study: High value manufacturing of enhanced property precision tubular products for biomedical and water applications		
Period when the underpinning research was undertaken: 2010 - present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Prof Phil Coates FREng	Professor of Polymer Engineering	Aug 1978 – present
Dr Fin Caton-Rose	Reader in Computer Aided Engineering	Jan 1998 – present
Prof John Sweeney	Professor of Polymer Mechanics	Jan 1995 – present
Prof Adrian Kelly	Professor of Process Engineering	Jan 1996 – present
Period when the claimed impact occurred: 2014 to 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Research into molecular orientation processing of polymers at Bradford has been exploited for biaxially oriented precision tubular products, leading to:

- jointly patented bioresorbable arterial and peripheral stents demonstrating class-leading precision wall thickness, radial strength and anti-thrombogenicity, together with a novel clean room manufacturing line at Arterius (2016).
- high pressure polyolefin pipes with superior long-term strength properties, and innovative continuous manufacturing technology (2019/20) outside diameter pipes for domestic and industrial applications, with SABIC.
- there has been a total of ~£16m investment in polymer engineering in the REF period.

2. Underpinning research (indicative maximum 500 words)

Professor Phil Coates (1978 – present), Dr Fin Caton-Rose (1998 – present), Professor John Sweeney (1995 – present) and Professor Adrian Kelly (1996 – present), who form part of the Polymer Interdisciplinary Research Centre, have extended the underpinning science of orientation processing of polymers by solid-phase deformation, and bridged the gap between the science and advanced manufacturing technologies. Our particular focus has been on die drawing of polymer profiles, with major developments in biaxially oriented tubes, the focus of this case study, and hot compaction of oriented polymer composite sheets. Over two decades our original EPSRC-funded research has progressed through partnerships with UK and global industry, investment by TSB/InnovateUK and further EPSRC funding (2009 onwards).

Our research has developed fundamental understanding of the mechanics of solid-phase deformation behaviour of polymers [R1,2; G2-6]. Our new constitutive relationships and physical modelling has been used to achieve molecular-related understanding of deformation and shape memory behaviour, enhancing computer modelling and control of structure [R1,3]. This has underpinned inventive steps in: (i) the design and implementation of die and mandrel geometries (controlling strain and strain rate fields), (ii) batch and continuous processes to exploit the significant property enhancements available through orientation control, for a range of tubular products with enhanced properties. [R1-4; G1,2,4,5,7,8,10,12].

Die drawing involves pulling solid polymers at temperatures above their glass transition but below their melting point, through converging dies and/or over mandrels (for tubular products, the focus here). This achieves controlled uniaxially or biaxially oriented structures. The physical properties increase monotonically with draw ratio (cross sectional area change imparted). Control of draw ratio thus allows products to be tailored for specific applications, for example die drawing of tubes to a selected combination of axial and radial draw ratios produces controlled radial strength tubes, important for avoiding vascular collapse [R4], or balanced biaxiality for thinner walled lighter weight pressure pipes. It also allows matching properties for in-body applications including blood compatibility, stiffness and strength of bone for joint or soft tissue fixations, and control of cavitation [R5, 6]. It is applicable for products in the micro to macro scales, e.g. the biaxially oriented tubular stents and pipes in this case study and all engineering polymers and products with various cross-sectional geometries.

Our research has not only extended fundamental understanding of deformation of polymers (applicable to more than processing) [e.g. R7c] but has also allowed us to innovate *process technologies* for controlled precision products. In 2015 a micro-scale high precision die drawing process for bioresorbable materials based on modified polylactic acids (PLAs) importantly provided the consistency required for manufacturing of medical devices, e.g. precision ~100μm wall thickness tubes for arterial stents [R4]. In 2018 a medium scale batch tube process exploiting novel mandrel-only drawing was developed in our laboratories. In 2020 this formed the basis of an industrial scale continuous process line for high pressure tubes.

Our underpinning research has further progressed by unique in-situ structural characterization of die drawing. Facilities designed and built by us are used in our joint laboratory established in 2015 in Changchun, China (Director P Coates, Programme Manager F Caton-Rose) [R7b], supported by a Royal Society Newton Advanced Fellowship (2015-19, PI Coates [R7d]). This in-situ research provides underpinning understanding of desired structures for property enhancement including the balance of axial and hoop properties which are important for manufacture of biaxially oriented tubes with controlled properties. Similarly, a Joint Research Laboratory with Sichuan (Director P Coates; programme manager F Caton-Rose) includes collaborative research on oriented polymer materials engineering, particularly for biomedical materials including PLAs. Outputs from this collaborative research underpin some of the impacts identified in Section 4.

Arterius and SABIC provide the two major impacts we focus on in this case study. They approached us because of our research strengths and unique facilities in solid phase orientation processing of polymers and our reputation for industrial collaboration in this area with a range of companies, from SME to global. Arterius approached us in 2010 to help make a novel arterial stent from a bioresorbable polymer, particularly targeting greater radial strength to avoid artery collapse, yet thinnest in class wall thickness (<100mm) to lower thrombogenicity and restenosis. The success of their initial collaboration with us established the viability of manufacturing, in our laboratories, the required precision tubes and hence the key focus of the company. SABIC came to us in 2014 to establish the viability of a scalable manufacturing process for high pressure polyolefin pipes to have class-leading, greatly enhanced long-term strengths.

3. References to the research (indicative maximum of six references)

R1. Ward IM, Coates PD, Dumoulin M [Eds] (2000). *Solid Phase Processing of Polymers*, PPS Series, Carl Hanser Verlag/Hanser Gardner Publications. [*This is the first and still the only research book on solid phase orientation processing].*

R2. Ward IM, Sweeney J (2012). *The Mechanical Properties of Solid Polymers* (3rd Edn), Chichester, Wiley. ISBN-13: 978-1444319507. P*rime research and teaching text*

R3. Coates P D., Caton-rose P., Ward I M, Thompson G., (2013) Process structuring of polymers by solid phase orientation processing, Science China-Chemistry 05/2013; 56(8): 1017–1028. https://www/doi.org/10.1007/s11426-013-4881-1

R4. Joint patent: Method of producing a tube for use in the formation of a stent, and such tube WO2014045068A1 - Kadem Al Lamee, Adrian Kelly, Philip D Coates, Glen P Thompson, Phil Caton-Rose, 27 March 2014

R5. Li Z, Ye L, Zhao X, Coates P, Caton-Rose F, Martyn M. High orientation of long chain branched poly (lactic acid) with enhanced blood compatibility and bionic structure. J Biomed Mater Res Part A 2015:00A:000–000. https://www.doi.org/10.1002/jbm.a.35640 2016 *[Sichuan Joint Lab supporting understanding of blood compatibility of oriented PLA, material used in stents]*

R6. Lu Y, Thompson G, Lyu D, Caton-Rose P, Coates P, Men Y, (2018) Orientation direction dependency of cavitation in pre-oriented isotactic polypropylene at large strains, Soft Matter 14(22), DOI: http://www.doi.org/10.1039/C7SM02446K *[Changchun Joint Lab supporting understanding of die drawing process for polyolefins, as in pipes]*
R7. Strategic Links with China: Polymer IRC, University of Bradford, 2019 http://www.polyeng.com/polyeng2/sbc-update-book-nov-2019.pdf: (a) International awards, p28-30) (b) Joint Labs, p18-19; (c) Royal Academy of Engineering project p11; (d) Royal Society Newton project p12-13

Grants

G1. TSB Proof of Concept Scheme: Arterius/TSB GBP47,000 03 2011 to 2012 *Development of bioresorbable polymeric stents by die drawing of extruded PLA tubing.*
G2. EPSRC EP/K029592/1 *Centre for Innovative Manufacturing in Medical Devices GBP*600,000 of GBP5,670,000 10-2013 - 09-2019 (with Leeds, Newcastle, Nottingham, Sheffield)
G3. Sinopec (China Petrochemicals) GBP330,000 *Polymer Deformation* 10/2013 to 9/2016
G4. EPSRC EP/L020572/1 *Smart Manufacturing of Medical Devices for soft tissue fixation* GBP826,000, 09-2014 to 03-2018
G5. EPSRC EP/L027011/1 *Capital Grant – Great Technologies: Advanced Materials for Healthcare* GBP3,420,000 01-2014 to 12-2023 Capital equipment
G6. Royal Academy of Engineering fellowship *Deformation and fracture of micromoulded specimens GBP*22,000 07-2014 to 05-2015 PI P.D. Coates; fellow - Dr Zhiyong Jiang (Changchun CIACCAS)
G7. SABIC *Die drawing of polymers* GBP232,000 07-2015 to 07-2018
G8. Arterius *Die drawing of stents technology* GBP53,000 2015-16 (novel manufacturing line design)
G9. Royal Society Newton Advanced Fellowship NA150222, GBP110,000 09-2015 to 08-2018 PI P.D. Coates; fellow - Prof Yongfeng Men (Changchun CIACCAS)
G10. EPSRC HIP EP/R024324/1 *Shape Memory polymer bone & soft tissue fixations* GBP904,000 07-2018 to 06-2022
G11. Sinopec (China Petrochemicals) *Solid phase orientation of polymers* GBP357,000 07-2018 -to 06-2021
G12. SABIC *Solid phase drawing of pipe* GBP50,000 2020

4. Details of the impact (indicative maximum 750 words)

Arterius: Based on the initial research which provided Arterius with confidence that desired stent property levels were achievable, the key impact has been to develop a bioresorbable high precision polymer stent for a demanding international market. The required stent property levels (especially radial strength, with wall thickness <100μm), together with an innovative manufacturing technology platform, represent the best-in-class arterial stent (Arteriosorb^{TM}). This is covered by a joint patent issued in 2014 [S1]. The manufacturing technology takes a polymer and greatly enhances its properties through a 'green' solid phase process – very high energy efficiency, no solvents, negligible waste, for tightly controlled, consistent high precision dimensions and tolerances, as required for such highly regulated medical technology products [S3,4,5]. Arterius acknowledge the importance of the polymer technology developed at the University of Bradford: *"This collaboration has been vital to our company in developing the leading quality of arterial stent, ArterioSorb^{TM} (http://arterius.co.uk). Without the Bradford team and facilities, this simply would not have been possible"* [S2].

Key impacts for Arterius:

1. **Viability of making bioresorbable stents by solid phase processing.** Producing the required quality bioresorbable polymer tubes for stents was successfully developed and demonstrated in the Bradford laboratories:
    a. Achieving required enhancements in accuracy and consistency of die drawn PLA tubes in Bradford, including die and mandrel geometry selection [S1, S3-5].
    b. Samples of PLA tubes produced for Arterius to use in external trials.

c. Training of Arterius staff in die drawing skills [S2,S3]. The Operations Manager at Arterius worked in the Polymer IRC laboratory at Bradford for extended periods, in 2014 (spread over 9 months) and 2015 (6 months, as part of an Arterius TSB. project), to learn new solid phase polymer orientation skills and develop expertise.
d. Support and evidence for external funding sought by Arterius, using the facilities and skills of the Bradford team [S2].

2. **Investment success.** Arterius have invested ~GBP7,500,000 in the development of the bioresorbable stent. This includes Venture Capital and Innovate UK support won to develop the required preclinical testing for product validation [S2].

3. **Manufacturing**. Bradford assisted a 3rd party engineering company to design and manufacture a Class 8 clean room installation at Arterius for precision tube die drawing - a "*very demanding manufacturing task, for Class 3 medical products, which have maximum scrutiny in terms of regulatory control." "This technology has been transferred most successfully from the University to the company, with a new facility in the company, allowing much improved repeatability with regard to tube quality and dimensional tolerance."* [S2]. Impacts as a result of the installation of the Class 8 clean room the Bradford team co-designed include:
    a. Manufacturing line installed at Arterius, Leeds in 2016.
    b. 95μm wall thickness tubes for arterial stents, with anti-inflammatory drug coating, manufactured successfully and consistently at Arterius.
    c. 500 stents per day production rate achieved, as required for the expected initial market for these very high added-value Class 3 medical products.
    d. The oriented tubes are laser cut to a strut pattern decided by fluid mechanics analyses, then have crimp fitted – all has been achieved for biaxially oriented polymer tubes.

4. **Enhanced next-generation products** – Arteriosorb™ bioresorbable stents have performance matching the best-in-class metal stents (from Abbott Inc) [S3, S4]. "*The collaboration with the Bradford team has made it possible to develop a class-leading bioresorbable coronary stent with superior radial properties using a controlled precision manufacturing process, opening the way for the next-generation of arterial stents*." [S2].

5. **Clinical trials** After completing in vitro development and preclinical testing of ArterioSorb™, clinical (human) trials of 40 patients, at 4 UK clinical centres had been arranged for March 2020, but have been seriously delayed by Covid-19, initially to April 2021 [S2].

SABIC is a global company making polymer materials. It is a leader in pipe production, one of the first to have Minimum Required Strength (MRS) pipes in classification MRS8 – a category which qualifies for 50-year lifetime of pipes. SABIC approached the Bradford team 6 years ago, to develop the process of biaxial forming of polyolefin pipes, because of our reputation and facilities in this area. SABIC have invested over GBP500,000 in continuing commercially sensitive research programmes in our laboratories since 2015.

Key impacts for SABIC:
1. **Viability of making high pressure pipe by solid phase processing.** A successful route has been established for high pressure pipe product production using solid phase forming at Bradford:
    a. demonstration of manufacture of sufficiently accurate and consistent die drawn PP and PE pipes in Bradford, including novel die and mandrel designs and materials [G7].
    b. Optimisation of process conditions [G12].
    c. Mandrel-only route for optimal biaxial property balance in pipes [G12].
    d. Extensive production of samples for SABIC to use in accelerated life testing for high pressure pipes (ISO 9080 standard) to demonstrate at least a 50-year life span.
    e. Development of skills of SABIC staff in tube die drawing. [G7, G12] with 6 x 2-week periods spent in the Bradford laboratories in the past 4 years [S6].

2. **Manufacturing.** Design and technology information from the research at Bradford has fed into a third-party engineering company in Italy for design and manufacture with SABIC of a full-scale continuous production line (~ 60m long) for 32-160mm outside diameter pipes. The first full scale production line is to be installed at a leading European PP pipe producer in Germany [S6].

3. **Enhanced products.** **"***We succeeded in producing polypropylene and polyethylene pipes with MRS values up to 15. This is an enormous improvement on what could be achieved with SABIC's resins to date, and much better than any product on the market."* [S6] – the current best Minimum Required Strength (MRS) is 8, so is almost doubled.

4. **Investment.** SABIC have invested over GBP3,000,000 in R&D to date in the development of the high-pressure pipe technology based on the Bradford programme, including polymer material development, accelerated testing and a continuous production scale manufacturing line [S6].

5. **Increased market confidence.** "*We are targeting to capture around 20% market share of PP pressure pipe by 2030*." [S6]. The new pipe product line (32mm to 160mm outside diameter) was due to be launched at an international event in Europe in September 2020, but this has had to be delayed because of the pandemic.

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1. University of Bradford and Arterius joint patent: K Al Lamee, A Kelly, P Coates, G Thompson, P Caton-Rose (2014) Method of producing a tube for use in the formation of a stent, and such tube WO2014045068A1

S2. Testimonial Letter from Managing Director, Arterius

"*The world-leading facilities and skills at Bradford helped my company to address our need to explore (i) solid phase orientation of polymers to develop a bioresorbable polymer stent with superior performance over class leading arterial stents, and (ii) a pilot route to precision, controlled manufacturing of stents...*
Thus, the collaboration with the Bradford team has made it possible to develop a class-leading bioresorbable coronary stent with superior radial properties using a controlled precision manufacturing process, opening the way for the next-generation of arterial stents".

S3. Arterius Website: UoB named as key research collaborators. http://arterius.co.uk/about-us/

S4. Development and Commercialisation of Bioresorbable Polymer Medical Implants, PPE19 international conference presentation, by Operations Manager, Arterius, July 2019.

S5. R&D SMART Award from the Innovate UK to Arterius."
"Arterius and University of Bradford have developed the proprietary technique of Die-Drawing to improve the mechanical properties. Excellent results have been obtained with financial support from Innovate UK-SMART Awards for proof-of-concept research and development, including preclinical assessment.
To date, a small-scale R&D die drawing system has been used. Whilst this proved sufficient for preclinical trials, there is now the need for a dedicated novel pre-production prototype die drawing system capable of producing high quality product in a reproducible manner for the for the manufacture of clinically approved coronary, peripheral, urology and biliary stents".

S6. Testimonial from Senior Scientist, SABIC (Netherlands)