**Institution:** University College London

**Unit of Assessment:** 3- Allied Health Professions, Dentistry, Nursing and Pharmacy

**Title of case study:** Development and launch of a new product, OCTASA1600™, for the treatment of inflammatory bowel disease

**Period when the underpinning research was undertaken:** 2008-2020

**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: |
|---|---|---|
| Abdul W. Basit | Professor, Pharmaceutics | 1997-Present |

**Period when the claimed impact occurred:** 2018-present

**Is this case study continued from a case study submitted in 2014?** No

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

Based on his research on targeted delivery to the gastrointestinal tract, Basit's group at UCL has developed the OPTImized COlonic RElease (OPTICORE™) system that allows highly specific colonic targeting. This combines Basit's proprietary PHLORAL™ technology with a further accelerator layer to promote drug dissolution. The technology was licensed to Tillotts Pharma for a mesalazine formulation and, following successful Phase III clinical trials, OCTASA 1600™ (1600mg mesalazine, once daily dosing) was launched in 2018. It is now prescribed across international markets for inflammatory bowel disease, a condition that affects approximately 7 million patients globally. Furthermore, the PHLORAL™ technology has led to the launch of the spin-out company Intract Pharma Ltd. with a current annual turnover of circa GBP1,000,000.

**2. Underpinning research** (indicative maximum 500 words)

The Basit group at UCL School of Pharmacy has made major contributions to the improvement of therapeutic efficacy in targeted oral formulations, particularly for delivery to the large intestine. The group has studied and identified the most pertinent physiological parameters that influence drug and medicament behaviour in the gastrointestinal (GI) tract including intestinal pH, content fluid volumes and composition, intestinal transit times and microbiota (**R1**, **R2**). The increase in pH in the colonic region has been suggested as a means of triggering site-specific release; however, the group demonstrated that, contrary to accepted beliefs, intestinal pH alone was a poor controller of site-specific tablet disintegration and hence drug release (**R3**). This enhanced understanding of the interplay between gut physiology and drug delivery enabled the development of novel means of triggering release in specific regions of the GI tract for the treatment of localised diseases such as ulcerative colitis (UC) (**R4**).

More specifically, the group explored sophisticated approaches to triggering release in the colon, leading to the development of PHLORAL™. This dual-trigger colonic delivery system simultaneously exploits both the pH change and alterations in the bacterial population along the GI tract, thereby providing a much more reliable means of providing colon-specific release (**R5**). Following the delivery system's license to Tillotts Pharma, a mesalazine formulation was developed by the Basit group with i) the PHLORAL™ technology and ii) an additional DUOCOAT™ accelerator mechanism beneath the PHLORAL™ layer resulting in the dual layer drug delivery technology, OPTICORE™ (**R6**). The PHLORAL™ intellectual property is assigned to UCL, the DUOCOAT™ technology that constitutes the accelerator layer is owned by UCL and Evonik and the OPTICORE™ technology, which combines the two, is owned by UCL and Tillotts. UCL and Tillotts have a royalty agreement in place for these technologies.

This REF2021 impact case study is distinct from the previous REF 2014 submission; the latter involved the development of three coating systems, one of which was PHLORAL™. Since that time, the Basit group has developed the OPTICORE™ technology, resulting in a mesalazine product (ASACOL 1600™, OCTASA 1600™ in the UK) which has passed Phase III trials, with subsequent regulatory approval. This new dosage form has now entered the market for the treatment of inflammatory bowel disease (IBD) in patients worldwide. The UCL spin out biotech company, Intract Pharma Ltd., was also launched during this time.

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

[R1] E.L. McConnell, H.M. Fadda, A.W. Basit. Gut instincts: Explorations in intestinal physiology and drug delivery. Int. J. Pharm (2008) 364:213-226. https://doi.org/10.1016/j.ijpharm.2008.05.012.

[R2] Ibekwe, VC, Fadda, HM, McConnell, EL Khela, MK, Evans, DF Basit, AW. Interplay between intestinal pH, transit time and feed status on the in vivo performance of pH-responsive ileo-colonic release systems. Pharm. Res. (2008) 25(8):1828-35. http://dx.doi.org/10.1007/s11095-008-9580-9.

[R3] McConnell EL, Short MD, Basit AW. An in vivo comparison of intestinal pH and bacteria as physiological trigger mechanisms for colonic targeting in man. J. Cont. Rel. (2008) 130(2):154-60. http://dx.doi.org/10.1016/j.jconrel.2008.05.022.

[R4] Ibekwe VC, Khela MK, Evans DF, Basit AW. A new concept in colonic drug targeting: a combined pH and bacteria drug delivery technology. Aliment Pharmacol. Ther. (2008) 28(7):911-6. https://doi.org/10.1111/j.1365-2036.2008.03810.x.

[R5] Varum, F, Freire, AC, Fadda, HM, Bravo, R, Basit AW. A dual pH and microbiota-triggered coating (Phloral™) for fail-safe colonic drug release. Int. J. Pharm. (2020) 583: 119379 https://doi.org/10.1016/j.ijpharm.2020.119379.

[R6] Varum, F, Freire, AC, Bravo, R, Basit AW. OPTICORE™, an innovative and accurate colonic targeting technology. Int J Pharm. (2020) 593:119372. https://doi.org/10.1016/j.ijpharm.2020.119372.

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

Inflammatory bowel disease (IBD) is a very substantial global problem, with approximately 6.8 million cases reported in 2017. The first line of treatment is usually oral, enteric-coated mesalazine tablets. Previous mesalazine products, however, showed sub-optimal therapeutic effects due to the inter- and intra-individual variability of the gastrointestinal tract. Without successful drug delivery, surgical removal of parts of the intestine can be the only remaining option; 25-40% of sufferers currently have all or a part of their colon removed. This can also necessitate the use of stoma bags that negatively impact quality of life.

PHLORAL™ and OPTICORE™, developed by the Basit group, represent the world's first dual trigger colonic coating technology. The coatings were the subject of patent applications in 2007 and 2012 respectively, which has since been granted worldwide, including publication of the European Patent in November 2017 **[S1].** The licence granted to Tillotts Pharma AG in 2007 for treatment of ulcerative colitis (UC) using mesalazine was the next generation of their current product ASACOL™, the market-leading product for treatment of this condition. Phase III clinical trials **[S2],** which commenced in August 2013 and were conducted with 823 patients with active UC, have demonstrated the effectiveness of the novel coating approach and its superiority to currently available pharmaceuticals in terms of consistent and precise colonic drug targeting. In addition, the new product is formulated with the highest dose of any oral product in the world, containing 1.6g of drug in a single dosage form. Specifically, the study "*showed that once-daily*

*ASACOL™ 1600 mg (mesalazine) is effective for the induction and maintenance treatment of mild to moderate UC with 22.4% of the enrolled patients in clinical and endoscopic remission at week 8 when treated with a 3.2 g/day regimen (2 tablets, once-daily). Data from the open label extension study showed that the extended treatment with 1.6 g/day (1 tablet, once-daily) is effective for the maintenance of clinical remission. At week 38, 70% of the patients, in remission after induction, maintained remission*" **[S3].** In the same press release, the Chief Scientific Officer of Tillotts Pharmaceuticals Johannes Speiss states, *"the development of ASACOL™ 1600 mg was made possible due to the incorporation of the new OPTICORE™ technology."* Following the success of the trials, the new generation ASACOL™ 1600mg product was successfully launched in 2018 as OCTASA 1600™ in the UK and ASACOL 1600™, YALDIGO 1600™ and ASACOLON 1600™ worldwide, including 19 EEA countries**.** While specific sales figures are commercially sensitive, the mesalazine formulations (the existing 400mg and 800mg enteric coated formulations and the novel 1600mg formulation) are together worth USD155,000,000 in annual sales **[S4]**. Zeria, the company that owns Tillotts Pharmaceuticals, state in their 2020 Business Report that despite a local sales decreases (in Japan), global sales of the ASACOL™ products increased from 2019 and ascribe that growth to the introduction of ASACOL™ 1600 **[S4]**.

In 2014, the PHLORAL™ technology was also licensed to Biokier Inc. for the formulation of the novel treatment for Type II diabetes, BKR-013. The Chief Executive of BioKier Inc. commented: "*The UCL Phloral™ coating, which allows for targeted delivery of pharmaceutical ingredients to the colon, is essential for the development of this drug*" **[S5].** The drug formulation, using the PHLORAL™ technology, has recently undergone a four-week triple blind study indicating significant improvement in insulin sensitivity within the treated patient group **[S6]**.

In addition, the development of PHLORAL™ and the advancements of treatments targeted for the gastrointestinal tract has led to the genesis of the spin-out company Intract Pharma **[S7]** following a GBP1,000,000 investment in 2015 from Cycle Pharmaceuticals based in Cambridge. Intract Pharma, founded by Professor Abdul Basit who also sits on the Board of Directors, is now a rapidly growing biotech which employs 9 members of staff as of September 2020, with a turnover of GBP1,000,000 per year. The PHLORAL™ technology is also currently accessed by 15 pharmaceutical companies by virtue of licensing deals, options or contracts to date. Licence payments to Intract Pharma are connected to fee-for-service contracts performed with external early-stage start-ups through to small/mid-range biotech firms and global large Pharma. Intract performs development studies to create novel products on behalf of these companies with partnerships across USA, Europe, India and Korea.

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

**[S1]** EP2659881B1 (2012) A delayed release formulation. Bravo Gonzàles, R. C., Buser, T., Goutte, F. J. C., Basit, A. W., Varum, F. J. O. (OPTICORE™). Published 2017.

**[S2]** D'Haens G.R. et al., Randomised non-inferiority trial: 1600 mg versus 400 mg tablets of mesalazine for the treatment of mild-to-moderate ulcerative colitis. Aliment Pharmacol. Ther. 2017; 46(3):292–302. https://doi.org/10.1111/apt.14164.

**[S3]** Tillotts Pharma AG announces launch of ASACOL™ 1600 mg (mesalazine) for ulcerative colitis. 2019. https://www.tillotts.com/news-events/pressrelease/tillotts-pharma-announces-launch-of-asacol-1600-mg/

**[S4]** Zeria 66th Business report 2020 https://www.zeria.co.jp/english/media/br2020_3_end.pdf

**[S5]** https://sciencebusiness.net/news/76510/UCLB-signs-exclusive-global-licence-with-BioKier-Inc.-for-colonic-delivery-of-gut-hormone-secretagogues

**[S6]** Biokier announcement on clinical study (2019) http://biokier.com/news/biokier-completes-four-week-clinical-study-with-bkr-013-at-pennington-biomedical-research-center-baton-rouge-la/

**[S7]** Testimonial Letter, Intract Pharma.