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Cover photo: Undifferentiated eukaryotic cells (see Regenerative medicine: energising technology evolution towards future medicine on page 19).



You are not alone

In 1905, the Spanish writer George Santayana penned the subsequently oft-quoted words *"Those who cannot remember the past are condemned to repeat it"*. With these words in mind, I recently leafed through earlier editions of the EIPG journal since its first publication in 2008, and came across the editorial I penned in the winter of 2014 (*Will they? Won't they?*).

Fast forward 2 years, and little seems to have changed. Global events continue to shake the industry – mergers and acquisitions and streamlining activity continue unabated, and the companies that were the subject of uncertainty amongst industrial pharmacists at the time, have once again, in recent weeks, made headlines, regrettably for the same reasons. Friends and colleagues find themselves once more looking with uncertainty and trepidation to their futures, one that is currently rendered even more uncertain by the latest European and global political events.

I also wrote back then, referring to the Delegated Regulation on safety features, *"While the broader strokes of this legislation that will have far-reaching effects throughout the continent are by now fairly clear to many, the minutiae of the process remain largely unknown, leaving actors in the pharmaceutical supply chain in a state of uncertainty, asking largely unanswered questions."* There are still many unanswered questions, brought regularly to my attention by industrial pharmacists in the pharmaceutical supply chain all over Europe. EIPG highlighted its concerns in a statement on the Regulation earlier this year, and recently elaborated upon them at the Interested Parties Meeting of the European Medicines Agency. The European Medicines Verification Organisation Progress Monitoring Monthly Report for the last 3 months is also disquieting. Whilst



progress is being made, two-thirds of countries are behind schedule, and one has to wonder how much time there will be to deal with issues – both technical as well as those related to everyday good practices – that will most probably arise when the entire system goes live EU-wide.

Industry is busy dealing with the technical aspects of the implementation of the Regulation, but it is the role of associations such as EIPG and its member organisations to deal with the professional matters. The British statesman Sir Winston Churchill, speaking in the House of Commons in 1935, said, *"Want of foresight, unwillingness to act when action would be simple and*

effective, lack of clear thinking, confusion of counsel until the emergency comes, until self-preservation strikes its jarring gong – these are the features which constitute the endless repetition of history." EIPG will do its utmost to take heed of this advice, and thus to prevent industrial pharmacists from feeling isolated in facing their challenges. Inspiration is to be found in our academic colleagues at the University of Camerino in Italy, who, notwithstanding the destruction wreaked to their beautiful city by the strongest earthquake to hit the peninsula in the last 30 years, came together only days later to witness the graduation of a new crop of pharmacists. Their courage and fortitude in looking to the future are an example to us all.

I extend to everyone the best wishes of EIPG for the season, and encourage you to look forward to a new year with confidence, for, I assure you, you are not alone.

A handwritten signature in black ink, which appears to read 'Claude Farrugia'.

Professor Claude Farrugia
President, EIPG

FORMULATION TECHNOLOGY CAN ENABLE ORAL DELIVERY OF NEW GENERATION MEDICINES FOR INFLAMMATORY BOWEL DISEASE

by Peter Timmins and Neil Mathias

Inflammatory bowel disease (IBD) is a complex, chronic inflammatory disorder that manifests as ulcerative colitis, a colon-centric disease, or Crohn's disease that affects mostly the distal ileum, colon, as well as other parts of the gastrointestinal (GI) tract. Treatment options range from small molecules to macromolecules (peptides, proteins and oligonucleotides) that target multiple therapeutic pathways, and dosed via injectable, oral or the rectal route for local bowel treatment. This review article describes some of the therapeutic drug classes and the delivery systems that aim to target drugs to the inflamed intestinal tissue. Clinically, many different distal ileum/colon targeting technologies have been studied, such as pH, time-based, pressure- and colonic microflora-activated drug release, as well as hybrid or dual-mechanism approaches with varied measures of success in IBD. The challenges these technologies face due to the dynamic, erratic environment of the inflamed intestinal mucosa can lead to highly variable or unpredictable release with a direct link to clinical success. However, newer improved delivery strategies are emerging that build on the past clinical lessons. With the possibility of integrating the newer macromolecular entities with precise targeting capability, the future prospects for innovative drug products to treat IBD more effectively looks very promising.

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Introduction

IBD is a chronic disorder which manifests in two forms; ulcerative colitis and Crohn's disease. The former affects only the large intestine and is a chronic, continuous disease affecting the mucosa and submucosa along the latter half of the transverse colon and the length of the descending colon to the rectum, with ulceration as well as inflammation. Symptoms include abdominal pain, rectal bleeding, diarrhoea, weight loss, fever and fatigue. Although mostly impacting the distal ileum and ascending colon, Crohn's disease can affect any part of the GI tract – mouth, oesophagus, stomach, duodenum, ileum, ascending colon, transverse colon, descending colon, rectum – and is characterised by small, scattered ulcers with symptoms including abdominal pain, fever, intestinal bleeding, steatorrhea (high fat in faeces) and risk of bowel obstruction or intestinal perforation¹⁻⁵. Although the drivers for development of the diseases is unknown, it is thought that these disorders arise from an abnormal immune response to an undefined environmental factor or factors. The sustained, erroneous immune response leads to the inflammation, lesions and tissue damage.

These diseases show exacerbation and periods of remission with treatment aimed to manage the acute episodes and to extend the remission periods by resolving symptoms, allowing healing of the inflamed, damaged mucosa and trying to prevent long-term disease complications. These complications can include perforation, colonic stricture and colorectal cancer which could require emergency surgical intervention. Currently, treatment involves the use of anti-inflammatories (aminosalicylates, corticosteroids) and immunosuppressants (e.g. azathioprine, 6-mercaptopurine, methotrexate) given systemically^{6,7}. The immunosuppressants are used in severe disease, with the aminosalicylates and steroids used for moderate disease. For



maintenance of remission, 5-aminosalicylic acid (5-ASA, also known as mesalazine), its dimer olsalazine or as sulphasalazine, both of which yield 5-ASA *in vivo*, is given orally as a modified (delayed) release or sustained release formulation to attempt to deliver drug more effectively to the disease site, especially in the case of ulcerative colitis. Oral modified release formulations of corticosteroids (e.g. beclomethasone, budesonide) are also available.

For treatment of inflammatory lesions in the rectum, corticosteroids or 5-ASA can be given as enemas, rectal foams or suppositories. Biologics, the tumour necrosis factor- α (TNF- α) antagonists infliximab, adalimumab, golimumab (and more recently for moderate to severe disease the integrin inhibitor vedolizumab where the TNF antagonists are contraindicated), have also become a valued therapeutic intervention for Crohn's disease and ulcerative colitis where non-biologics therapies are insufficiently effective⁸. If disease continues to progress despite treatment, colectomy may be necessary.

There remains a need for improved therapies that are highly effective, well tolerated and convenient for patients. As a treatment strategy, TNF- α antagonists are used when small molecule treatments fail, although up to 40% of patients will fail to respond and a further 50% of such patients who do show a response will fail within the first year of treatment⁹. These TNF antagonists can be associated with increased risk of infections, hypersensitivity reactions, immunogenic responses, and a number of other rarer but serious adverse events. Patients treated with corticosteroids and immunosuppressants have increased risk of infections and those treated with azathioprine have increased risk of developing lymphoma.

Given the continued unmet need, a number of novel small molecules

as well as complex molecules, including antisense oligonucleotides, peptide and protein biologics, and alternate routes of delivery (to current parenteral) are being explored as add on or alternate and replacement therapies for the current care options. Many of these newer complex molecules suffer from significant biopharmaceutical and delivery issues, requiring innovative formulation technologies to overcome the delivery barrier and enable their use by patients. This review will not cover the myriad of experimental GI targeting formulation approaches that are described in the literature where only *in vitro* or animal *in vivo* studies are used, but will focus on those drug delivery technologies where drug delivery has been applied or explored in human subjects.

Challenges with oral targeted delivery to the lower GI tract

Rectal delivery remains an option for treatment of IBD affecting principally the rectum and the most distal parts of the descending colon, where conventional approaches would involve suppositories or enemas. The latter can perhaps achieve greater spreading of medication and may, therefore, better treat disease that is not just confined to the rectal area but still deliver a high concentration of drug at the disease site. However, the ability of rectally delivered medication to access disease sites other than those in close proximity to the rectum is obviously constrained.

The treatment of Crohn's disease or ulcerative colitis by oral delivery of a therapeutic agent into the distal ileum and/or the colon provides the most practical strategy to treat inflamed tissues at a site or sites not accessible via introduction of medication via the rectum. A critical attribute is that it requires reliable mechanisms for delaying liberation of drug until the delivery system has traversed the unaffected regions of the GI tract, releasing

high concentrations of the drug where needed. If the drug is liberated higher up in the GI tract, there is a likelihood of undesirable systemic absorption, and even if it is not absorbed into the systemic circulation, it will still undergo dilution with GI contents, thus potentially reducing the concentration of drug available at the disease site. Therefore, an ideal delivery system for IBD has to survive the (usually) low pH environment of the stomach, resist inactivation by digestive enzymes, and transit intact through the small intestine, and via suitable trigger mechanism deliver drug to the affected area in the distal ileum and into the colon for the treatment of Crohn's disease, or solely in the colon (the transverse and descending colon) for the treatment of ulcerative colitis. Drug release triggers can be environmental pH dependent, enzymatic (including colon bacterial enzymes), time-based or pressure dependent. Delivery strategies for targeting drug release in the lower GI tract are given in **Table 1**. Challenges faced by drug delivery technologies and the physiological impacts are listed in **Table 2**. **Table 3** describes technology approaches that have been explored in humans along with their pros and cons.

Newer oral therapeutic entities in IBD and the role of delivery technology

Phosphatidylcholine

The therapeutic potential of topical phosphatidylcholine in ulcerative colitis is based on the fact that patients with this form of IBD have low intrinsic phosphatidylcholine content in their colonic mucus, distinct from healthy subjects or those diagnosed as having Crohn's disease^{10,11}. With this impaired barrier, intestinal bacteria can trigger a local immune response leading to inflammation and ulceration¹². Administration of phosphatidylcholine orally for delivery to the colon might restore the barrier properties of the colonic



Table 1: Delivery strategies to target drug liberation in the lower GI tract

Technology approach	Comment on trigger mechanism
pH-trigger: polymers with pH-dependent solubility (enteric coated systems)	Uses patient's intestinal pH to dissolve coating polymer around dosage form to release drug. Acidic functional group-substituted polymers that only dissolve above pH 6.0–6.5 (e.g. hydroxypropyl methyl cellulose acetyl succinate, methacrylic acid copolymer). Can be applied to conventional tablet or capsule formulation of drug in conventional pan or fluid bed coater
Time-dependent release	Cellulosic or gum-based outer "shell" to conventional tablet dosage form containing the drug, can be applied by tablet-in-tablet compression equipment or could be applied in a coating pan. Provides for a 5–6 hour erosion time of the shell polymer before drug is released. With typical average gastric emptying times for non-disintegrating single unit systems, this should deliver the contained drug to the lower GI tract
Colonic microflora-controlled	Activated by enzymes secreted by colonic bacteria. These enzymes degrade the polymer coating around the dosage form and liberate the contained drug. The coatings can be natural polysaccharides (e.g. amylose, chitosan, pectin, alginate) or synthetic (e.g. azo-polymers)
Osmotic pumps	Usually considered as extended-release systems, but typically these systems exhibit a delay before drug release is initiated, which can be manipulated to begin the extended release delivery in the distal small intestine
Pressure-controlled systems	These usually function by having a thicker enteric coat (typically methacrylic acid copolymer) than used for pH-dependent delivery or other water-insoluble polymer coat that is disrupted externally due to peristaltic waves in the colon or internally due to the dosage form imbibing fluid and the consequent build-up of pressure rupturing the coating. Performance is dependent on controlling film thickness and its integrity (pits, fissures, other flaws)
Hybrid approach – combine two trigger mechanisms	Can be pH-dependent plus microflora-controlled, pH-dependent plus time-dependent, or time-dependent plus microflora-controlled. These combine the advantages and disadvantages of the single trigger, but offer a back-up trigger should one not function properly in any given situation.

mucus with beneficial outcomes on disease. Phosphatidylcholine is a slow wetting amphiphilic surfactant that, in a conventional immediate-release oral formulation, may be liberated prior to reaching the target inflamed intestinal site, thereby reducing its effectiveness. An optimised formulation developed by Lipid Therapeutics, known as LT-02 and based on 94% soy lecithin concentrate, is presented as granules coated with methacrylic acid–methyl methacrylate copolymer 1:2 (Eudragit S™), providing for

polymer dissolution and phosphatidylcholine release once the granules encounter an environment of pH 7.0 or greater, targeting the distal ileum^{13,14}. In a Phase 2b trial in 156 patients having inadequate response to mesalazine, LT-02 added on to existing therapy showed statistically significant improvement in disease relative to placebo¹⁴. It appears the product may help with those patients already receiving approved doses of mesalazine who continue to experience flares of disease activity. Phase 3 trials have commenced in

Europe and are planned to be initiated in the USA during 2016 through licensees Dr Falk GmbH and Nestlé Health Science^{15,16}. If trials are successful, the product could receive regulatory approvals in 2019¹⁵.

Antisense oligonucleotides: alicaforsen, cobitolimod (DIMS0150) and mongersen

Therapeutic antisense oligonucleotides (ASOs) are synthesised short lengths of DNA or RNA (typically 15–20 bases), chemically modified to improve

Table 2: Challenges with oral lower GI tract targeting

Physiological variable	Challenge to delivery technology
High variability of inter- and intra-subject gastric motility	Varied gastric emptying time for dosage form will variably accelerate or delay time to trigger (pH, pressure, enzymatic-based systems) or for time-dependent triggered systems will result in premature (if retained too long in stomach) or failure of delivery (if time for complete transit through GI tract is short)
High variability in intra- and inter-subject GI pHs	Can result in variable premature or failure of trigger for pH-dependent systems
Low water, viscous liquid colonic environment	May challenge performance of systems requiring good water environment for trigger activation, e.g. erosion-based time-dependent trigger systems
Impact of disease state (e.g. degree of inflammation)	May modify GI pH and motility with dosage form performance risks as outlined above. May alter colonic microflora, which may affect systems triggered by colonic bacterial enzymes
Co-therapies	IBD patients may also be treated with antacids, proton pump inhibitors or H2-antagonists which will impact the performance of pH-dependent systems leading to premature triggering and drug release. Patients also treated with probiotics might have an altered gut microflora which might impact the performance of systems triggered by the action of enzymes secreted by gut bacteria



Table 3: Comparative properties of lower GI tract targeting technologies

Technology	Mechanism	Pros	Cons
pH-dependent polymer coating, e.g. methacrylic acid copolymer, hydroxypropyl methyl cellulose acetate succinate, Sigma-Tau polymers, ColoPulse	pH-dependent solubility of polymer means coating remains intact at typical gastric and duodenal (low) pH. Dependent on grade of polymer selected, the coating can be tailored to begin dissolving at pH 5.5 or higher	Very established approach. Conventional manufacturing equipment employed. Already applied in several marketed products and for newer entities currently in clinical development	High variability in delivery and hence pharmacokinetics, timing of drug release dependent on gastric emptying and intestinal transit time, hence uncertainty of timing and specific site of drug release. Performance is sensitive to factors affecting gastric motility and pH – food, antacids, proton pump inhibitor or H2 antagonist use, which could lead to premature drug release
Time-dependent release, e.g. TimeRx, Cosmo MMX technology	Slow release swellable polymers; hydrophilic/hydrophobic polymers	Variant of conventional equipment used for manufacture. Already applied in marketed products	High variability in delivery and hence pharmacokinetics, timing of drug release dependent on gastric emptying and intestinal transit time, hence uncertainty of timing and specific site of drug release. Performance is sensitive to factors affecting gastric motility – food, disease state which can result in premature release or failure of release of drug
Pressure-controlled systems e.g. PCDC (Kyoto Pharmaceutical University)	Impermeable polymer film (ethylcellulose) coated drug-containing core that is fluid at body temperature (polyethylene glycol 1000). These “balloons” can resist pressures due to motility in the stomach and small intestine but rupture in the colon to release drug for local action	No dependency on pH or microflora	Complex manufacturing. High variability. Narrow window for optimisation of coat thickness to assure appropriate pressure sensitivity, especially for smaller size dosage forms
Microflora controlled, e.g. Alizyme COLAL, Astellas CODES	Colonic bacterial enzymes degrade coating around dosage form to release the drug	A colon-specific targeting technology, as relies on colonic bacterial activity	Sensitivity to patient variability in capability of their colonic microflora, hence some uncertainty in how reliable the technology is dose to dose, patient to patient. May be sensitive to co-administered probiotics
Hybrid approaches	pH-dependent solubility of one polymer, colon enzyme targeting of second polymer. Back up trigger mechanism is available should one not function well	Potential for greater reliability of release and targeting along with reduced variability	Added complexity; still sensitive to disease state and co-administered therapy effects?

chemical and metabolic stability, that can act therapeutically by binding to mRNA at base pair complementary sites and inhibit expression of the inflammatory mediator proteins encoded in the mRNA. The down regulation of proteins involved in disease mechanisms by ASOs offers an approach to therapy, assuming adequate amounts of the ASO can reach the target mRNA¹⁷. Three agents in this class, alicaforsen, cobitolimod (DIMS0150) and mongersen, have entered clinical trials for the treatment of IBD¹⁸.

Alicaforsen inhibits intercellular adhesion molecule 1 (ICAM1) protein expression. ICAM1 is an inducible transmembrane

glycoprotein of the immunoglobulin superfamily. The induction of ICAM1 expression occurs in response to pro-inflammatory cytokines and mediators and it is involved in various ways in inflammatory processes, such as leucocyte recruitment and activation. ICAM1 is over-expressed in ulcerative colitis and experimental models of colitis have suggested that antisense ICAM inhibition approaches could be effective in treatment¹⁹.

Although seemingly promising when dosed parenterally in a small (20 patients) placebo-controlled pilot study, intravenously or subcutaneously administered alicaforsen did not show clear

efficacy in two subsequent double-blind, placebo-controlled Phase 2 trials^{20,21}. It was suggested that adequate exposure may not have been achieved and also that sufficient drug was not reaching the target sites in the gut from the systemic circulation¹⁸.

In consideration of this, and that some rectally delivered drugs are effective in distal forms of ulcerative colitis and have a good safety profile²², it is interesting to note that a rectal enema formulation, containing 240mg of alicaforsen in 60mL of an aqueous hydroxypropyl methylcellulose vehicle has been studied and appears therapeutically effective. Although in a placebo-controlled study the primary



endpoint was not attained, a statistically significant percentage reduction in Disease Activity Index (DAI) at week 6 of therapy relative to baseline DAI, there was a prolonged reduction in mean DAI in the treatment arm relative to placebo for weeks 18–30 post-start of treatment²³.

In a bioavailability study of rectally delivered alicaforsen, it was found that colonic tissue levels of drug were orders of magnitude higher than those found in plasma. The plasma levels of alicaforsen found represented 0.6% bioavailability of the drug²⁴. The low systemic exposure and high tissue levels may support the use of topical ASOs to enable efficacy whilst avoiding the infusion-related reactions seen with intravenous therapy, which may be associated with cytokine release syndrome²⁵ (a systemic inflammatory response similar to that seen with severe infections, with symptoms including fever, hypotension and rigors). Alicaforsen enema has been licensed by its innovator Ionis Pharmaceuticals (formerly Isis Pharmaceuticals) to Atlantic Healthcare who have recently initiated Phase 3 clinical trials in pouchitis, which is inflammation of an ileal pouch surgically made out of small bowel and created in the management of ulcerative colitis patients who have undergone surgical removal of the large bowel²⁶.

Multiple immune system pathways appear to operate in IBD and so alternate targets for potential therapeutic intervention can be beneficial. Cobitolimod (DIMS0150, Kappaproct[®]) induces the activation of the Toll-like receptor 9 (TLR9) pathway in the effector cells present on mucosal surfaces resulting in the localised production of anti-inflammatory cytokines such as interleukin-10 (IL-10). This also restores the subject's sensitivity to steroids²⁷. Cobitolimod is a 19 base pair ASO that is not significantly systemically absorbed when administered topically inside the large intestine. The local action and limited absorption may

contribute to a favourable therapeutic index²⁸. In one study in eight chronic active ulcerative colitis patients, a single 30mg dose in 50mL of vehicle topically to the colon epithelium during colonoscopy (in one subject three doses each 4 weeks apart) was administered via a spraying catheter. After treatment, there was positive clinical response. Endoscopy showed improvement at week 1, and by week 12 post-treatment 86% of subjects exhibited a clinical response with 71% in remission.

Subsequently, steroid doses could be reduced²⁷. In a small, placebo-controlled study, 30mg of cobitolimod was administered rectally in 50mL of water for injection via a catheter inserted in the bowel lumen. Although a sustained clinical improvement in disease in subjects in the treatment group was seen, the statistical power limitations of the study did not allow proof of primary or secondary endpoints²⁹. Going forwards, trials utilising the ability to select patients most likely to respond to cobitolimod treatment by use of biomarkers and so improve its therapeutic utility have been suggested³⁰.

Based on experimental models, it is suggested that IBD may be associated with an inappropriate and marked immune response directed against normal intestinal microflora, wherein the counter-regulatory control mechanisms are malfunctioning. Transforming growth factor- β 1 (TGF- β 1, a potent immunosuppressant, through a series of steps activates Smad2 and Smad3 which works in concert with Smad4 in the nucleus to regulate many genes. The endogenous Smad inhibitor Smad7 blocks activation of Smad2/Smad3 that is typically overexpressed in intestinal tissue samples examined from patients with IBD. Hence, inhibiting Smad7 could restore the activity of TGF- β 1 and favourably modulate inflammatory processes³¹.

Mongersen (GED-0301), a 21-base ASO that acts as a Smad7

antagonist, tackles IBD by a different pathway to the two ASOs already described above. It is being investigated for the treatment of Crohn's disease³². It is administered orally as a formulated tablet dosage form with a film coating having pH-dependent solubility, methacrylic acid-methyl acrylate copolymer, which starts to dissolve and release drug from the dosage form at pH 6.6–7.2, delivering mongersen to the terminal ileum and ascending colon^{32,33}. Phase 2 data was positive, with 72% of patients dosed at 160mg mongersen a day achieving a clinical response and 65% of that group were in remission at 2 weeks, statistically significant from placebo treatment and favourably comparing with treatment with biologics³⁴. The rights to mongersen were acquired by Celgene Corporation in early 2014³⁵, and is currently readying for a Phase 3 trial start in Crohn's disease³⁶, and a Phase 2 trial in ulcerative colitis is recruiting subjects³⁷. Oral mongersen offers a distinct compliance and convenience advantage compared to rectal or invasively dosed ASOs.

Janus kinase inhibitors: tofacitinib

The janus kinase (JAK) family of proteins (JAK1, JAK2, JAK3 and TYK2) are one subgroup of the non-receptor protein tyrosine kinases that are important in cell growth, survival, development and differentiation. They are critically important for immune system cells and haematopoietic cells. Based on human clinical observations and mouse models, mutations of TYK2 and JAK3 result in immunodeficiency; deletions JAK1 or JAK2 in mice are lethal. JAK2 mutations in humans appear to be associated with haematological malignancies. Therefore, these kinases have become interesting therapeutic targets for the treatment of inflammatory disease and leukemias³⁸.

Tofacitinib (CP-690550, also formerly named tasocitinib but changed in 2011 to avoid confusion



with other similar sounding generic and branded medicinal product names) is a potent small molecule inhibitor of the JAK family of kinases with some selectivity over JAK1 and JAK3 relative to JAK2, and with more limited inhibition of TYK2. It is rapidly and well absorbed (t_{max} 0.5–1 hour post-dosing), with dose-proportional systemic exposure over the range 0.1–10mg) and an absolute bioavailability of 74%. It has an elimination half-life of about 3 hours, requiring it to be dosed orally twice daily^{39,40}. In a multicentre, double-blind, placebo-controlled Phase 2 study in 194 patients with moderate to severe active ulcerative colitis, subjects were randomised to active drug 0.5, 3, 10 or 15mg or placebo twice daily for 8 weeks. At the 8-week time point, there was a clinical response in 78%, 61%, 48% and 32% of subjects in the 15, 10, 3 and 0.5mg dose groups, respectively, with a 48% response in the placebo group; clinical remission was seen in the 15, 10 and 3mg dose group⁴¹. This positive data allowed progression to Phase 3 studies, of which OCTAVE Induction 1 and OCTAVE Induction 2 trials indicated that the primary endpoints were met⁴². At the time of writing, the detailed results of these trials are yet to be published. Two further Phase 3 trials remain in progress.

These trials used an immediate-release formulation dosed twice daily. There may be an advantage in convenience to patients from a product tailored for once daily dosing, achieved through a modified release formulation approach, and indeed such a product has been developed using proprietary extruded core osmotic controlled-release technology^{43,44}. The pharmacokinetic profile of this product was confirmed as likely being suitable to allow once daily dosing, with bioequivalence demonstrated based on area under the curve and C_{max} 90% confidence intervals, with t_{max} being delayed from 0.5–2 hours for the immediate-release formulation to 4 hours for

the modified-release product, and elimination half-life being extended from 3.2 to 5.9 hours⁴⁵. This modified-release product has not been reported as yet being studied in patients with IBD and it will be interesting to see if formulation technology makes a difference to clinical outcome compared with the immediate-release product. Extended-release systems, due to the limited small intestine residence time relative to the overall release time of drug from the product, tend to deliver significant amounts of drug to the terminal ileum and colon and could exert a beneficial local effect.

Two other JAK inhibitors are in early stage trials for treatment of inflammatory GI disease, filgotinib (GLPG0634) in Crohn's disease and peficitinib (ASP015K)³⁹. Although the detailed results of both trials were awaited at the time of writing, the study with filgotinib, using a conventional formulation, achieved the primary endpoint of clinical remission: the percentage of patients achieving a Crohn's DAI (CDAI) score lower than 150 was statistically significantly higher in patients treated with filgotinib versus patients receiving placebo⁴⁶.

Ozanimod

Ozanimod (RPC1063) is a small molecule, potent, orally bioavailable selective sphingosine1-phosphate (S1P) receptor antagonist. S1P has physiological functions including control of lymphocyte trafficking, heart rate and vascular tone through its interactions with five receptors, S1P1–S1P5. The greater affinity of ozanimod for S1P1 and S1P5 over the other S1P receptors means that it rapidly induces a reversible reduction in circulating lymphocytes with a potential favourable side-effect profile relative to less selective antagonists⁴⁷. The reduction in circulating lymphocytes leads to anti-inflammatory activity by inhibiting migration of pathologic lymphocytes to sites of inflammation⁴⁸. Clinical remission was seen in 16% of patients on a

1mg dose of ozanimod against 6% on placebo at 8 weeks, and histological remission was seen at week 32 in 31% of patients on ozanimod 1mg against 8% on placebo^{48,49}. The S1P antagonists represent an interesting case for delivery using a novel rapid-release formulation technology as the anti-inflammatory activity may require good systemic availability (rather than local effects) and the criticality of having rapid lymphocyte repopulation kinetics (to avoid infections) means sustained plasma levels may be undesirable.

Laquinimod

Laquinimod (TV-5600) is under development for the treatment of both primary progressive and relapsing remitting multiple sclerosis, as well as being investigated for the treatment of Huntingdon's disease⁵⁰. Although the molecular target laquinimod acts upon is not noted, it appears that it is able to modulate inflammatory processes through affecting cytokine production. In animal models, laquinimod reduced pro-inflammatory TNF- α , IL-17 and IL-12 levels and increased anti-inflammatory TGF- β and IL-4. Pro-inflammatory IL-17, IL-3 and granulocyte-colony stimulating factor levels were reduced in human peripheral blood mononuclear cells isolated from healthy human subjects on incubation with laquinimod⁵¹. Laquinimod is rapidly absorbed (t_{max} approximately 1 hour post dose) when dosed orally and has high bioavailability⁵². In a placebo-controlled Phase 2 study in Crohn's disease, there was improved remission of disease relative to placebo⁵³. Although being further investigated in multiple sclerosis and Huntingdon's disease, no other trials of laquinimod in GI inflammatory disease are listed on clinicaltrials.gov but the authors of the paper on the Phase 2 trial talk of plans for a Phase 3 study⁵³. As the therapeutic effects of laquinimod may be effected systemically rather than locally, the



role of rapid or extended release technology for this molecule is not clear.

Oral anti-TNF antibodies: AVX-470

Avaxia Biologics have explored the utility of a novel antibody therapeutic, AVX-470, given orally in the treatment of ulcerative colitis. AVX-470 is an anti-TNF polyclonal antibody generated by immunising pregnant dairy cows with recombinant human TNF. Immunoglobulin purified from the colostrum from these cows contains the antibody and has *in vitro* activity comparable to that of the established anti-TNF parenterally administered monoclonal antibody infliximab⁵⁴. In a placebo-controlled, double-blind ascending-dose Phase 1 study in patients with active ulcerative colitis, AVX-470 formulated as a solid dosage form with an enteric coating that has solubility at >pH 6.0 was evaluated⁵⁵. Although the antibody is described as stable in the GI tract, it is indicated that the enteric coating assures better stability and hence more effective delivery of drug to the disease site⁵⁶. However, Avaxia claim their coating polymer starts to dissolve at pH 6.0 which can mean drug might have been delivered from the dosage form well before it has reached the ileum.

Drug delivery technology and inflammatory GI disease

Novel GI-targeted site drug delivery technologies

Although they are not new generation therapies, budesonide, prednisolone metasulfobenzoate sodium, 5-aminosalicylic acid and other small molecule therapeutics showcase the functionality and effectiveness of various innovative delivery technologies described in this section that could be used to create medicines to treat IBD. They exemplify technology that could be applied to the new and emerging agents for local and/or systemic effects in the treatment of Crohn's

disease and ulcerative colitis. Some of the new therapeutic agents will be discussed in the light of these technologies. In this article, delivery technologies that have been tested in clinical studies will be discussed to highlight their success and failures in IBD.

Pressure-controlled colon delivery capsule

Researchers at Kyoto Pharmaceutical University have described the human *in vivo* performance of a luminal pressure-controlled colon delivery capsule (PCDC)⁵⁷. These are based on a moulded core containing the drug dispersed in a hydrophilic suppository base material (polyethylene glycol 1000), where the moulded core (formed in stainless steel mould like suppositories) is equivalent in size to either a size 0 or a size 2 capsule. During the moulding operation, a rod is inserted into the molten drug excipient mixture to manage volume changes during solidification of the molten mass, and on removal of this rod, the hollow core is sealed at its open end with polyethylene glycol 1000. The core is then coated with the hydrophobic polymer ethylcellulose. It was hypothesised that this technology works by melting of the core after dosing, the ethyl cellulose swells or "balloons" in the GI lumen but the light luminal pressure is insufficient to rupture it. However, it is proposed that in the colon, pressures due to motility are higher here and the low fluid content leads to rupture of the "balloon" and release of the drug⁵⁷. The amount (thickness) of ethylcellulose coating must be sufficient to prevent premature rupture prior to delivery to the colon (a hardness of 2N for size 0 dosage forms is required), but if the ethylcellulose coat thickness is too great then rupture of the balloon may entirely fail to occur.

In a study in a small number of human subjects, it was demonstrated that the delay in first

detection of the model drug caffeine in saliva was consistent with that of colon arrival time, based on GI magnetomarkergraphy⁵⁷. However, direct simultaneous correlation of dosage form location, liberation of contents and drug pharmaco-kinetics was not verified. Variability of salivary caffeine pharmaco-kinetics was quite high, indicating that although a mean delivery time consistent with colon arrival is feasible, even in the small study drug delivery for some subjects would have occurred somewhat prior to colon arrival. Making dosage forms smaller than size 0 capsule size equivalent may be challenging for this technology also, as the coating thickness window for optimal delivery may become narrower than for larger dosage forms. For the smaller dosage forms, a thicker coat is required but this also risks making the dosage form too hard for colonic pressure to trigger release of the drug in the desired regions⁵⁷. These formulation variables and the complexity in manufacture may pose a significant challenge for commercialisation of this approach.

ColoPulse

Although based on a pH-dependent soluble polymer, the ColoPulse coating technology was developed to overcome the problems associated with pH-dependent coating approaches to delivery to the ileo-colonic region. For delivery systems based on enterosoluble polymer coating only (methacrylic acid-methyl methacrylate copolymer (1:2), Eudragit S™), slow dissolution of polymer can occur with the initiation for release at a pH >7.0, although the dosage form may only reside for a short period of time. To ameliorate this, reducing the coating polymer thickness or choosing a polymer with a lower pH for onset of dissolution can result in faster release and longer residence time, however, it could also lead to premature delivery or highly variable delivery, which may lead to



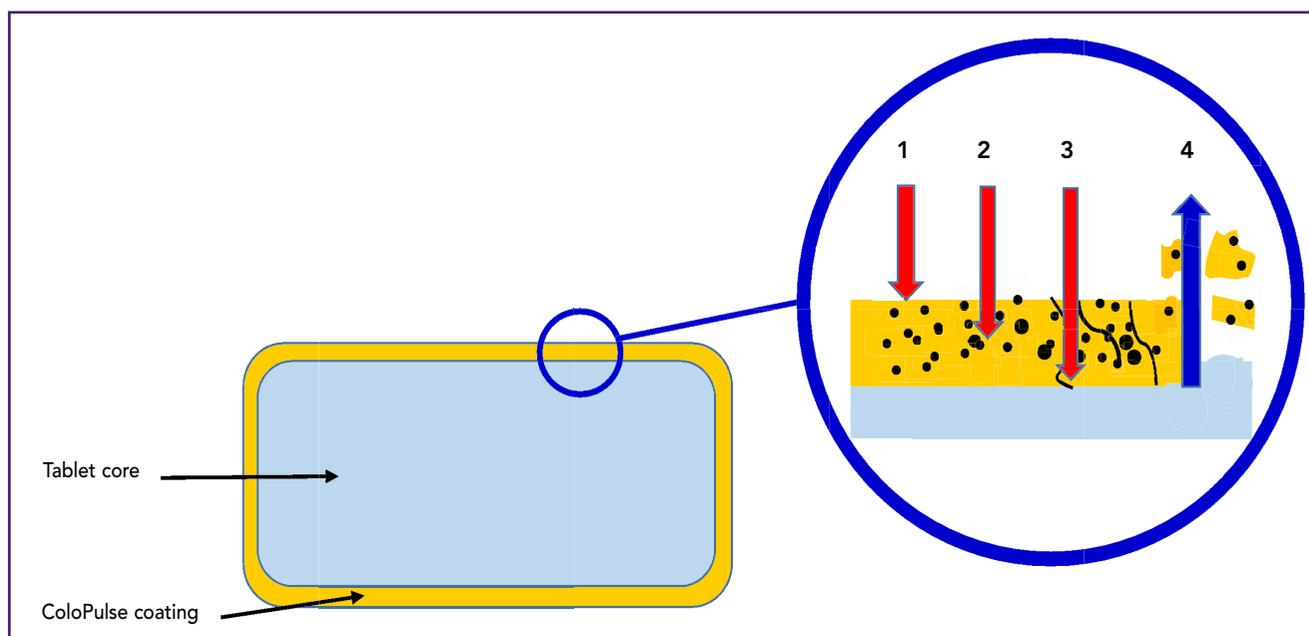


Figure 1. ColoPulse technology. 1. In an environment where pH is below threshold pH for polymer dissolution, medium does not penetrate, no effect. 2. In an environment where pH is above threshold pH for polymer dissolution, medium penetrates film coat and initiates swelling of disintegrant. 3. Swelling of disintegrant develops cracks in polymer coat, accelerates polymer coat dissolution. 4. Dissolution of drug from core at target site.

failure of delivery. ColoPulse coating is designed to improve the rate of dissolution of pH-dependent polymer once the appropriate pH environment (desired site of delivery) is encountered and offer true pulsatile release⁵⁸.

The ColoPulse coating uses methacrylic acid-methyl methacrylate copolymer (1:2) but the pH-responsiveness is enhanced by the incorporation of a swelling disintegrant (croscarmellose sodium) in the coating. Once the pH at which the polymer starts to dissolve is encountered, fluid reaches the disintegrant particles which can then swell and promote the formation of cracks in the polymer film which allows fluid penetration into the coat and encourages rapid polymer dissolution⁵⁸ (see **Figure 1**).

The level of disintegrant employed is such that it does not offer opportunity to provide a pathway of closely neighbouring particles that would offer a ready pathway for fluid penetration to the tablet core prior to polymer dissolution initiating. This is described as a non-percolating lattice, with the disintegrant amount

being below the percolation threshold above which its typical disintegrant properties would dominate⁵⁹.

The core tablet composition can influence the performance of the ColoPulse technology. The core is required to have some degree of swelling itself; including a water-soluble excipient, glucose, impaired pulsatile release performance compared with having slightly swelling microcrystalline cellulose in the core. Alkaline or acidic core tablet ingredients also impaired pulsatile performance. An acidic excipient, citric acid, prevented drug release and alkaline excipients, sodium bicarbonate or sodium benzoate, reduced the time to drug release, which might manifest as premature drug delivery *in vivo*⁶⁰. A barrier subcoat (e.g. a neutral polymer such as low viscosity hydroxypropyl methyl cellulose) may be required in the case of active ingredients or excipients that affect the pulsatile performance of the ColoPulse coating⁶⁰.

The ColoPulse technology was originally validated in human volunteers and shown to release

drug in the ileo-colonic region independent of transit times and once pH 7.0 environment is encountered⁶¹. It was found to perform in a comparable way in the disease-state in patients with Crohn's disease⁶². This robustness is important as small intestine transit time is prolonged in patients with active Crohn's disease or ulcerative colitis compared to healthy subjects or to patients with quiescent disease⁶³. ColoPulse tablets also showed no sensitivity to food other than that expected from the known effect of food on GI transit time⁶².

The feasibility of the application of ColoPulse to newer therapies employed in the treatment of IBD possibly enabling the oral delivery of the anti-TNF monoclonal antibody infliximab for topical effect in the colon has been demonstrated. A stable tablet dosage form with required robust pH-dependent drug release, having a profile compatible with colonic delivery, was produced⁶⁴.

COLAL

COLAL is a microflora-activated delivery system that uses glassy

amylose as the microflora-activated trigger polymer. It was developed to overcome the shortcomings of simply relying on a dosage form coated with glassy amylose to delay drug release⁶⁵. Glassy amylose is not degraded by human amylase enzyme in the GI tract, but is digested by colonic bacterial enzymes. Glassy amylose alone is believed to imbibe fluid in the upper GI tract and swell, leading to weakening of the coat integrity and premature partial or complete release of the drug.

The inclusion of a second polymer to control the swelling is required to better target drug release from the dosage form to the colon⁶⁶. By adding a more hydrophobic cellulose ether polymer to the glassy amylose in the ratio 4:1 and 5:1, along with a plasticiser, dibutyl sebacate and applying this to the drug-containing formulation in a fluid bed coater to a weight gain of 10–20% w/w, a delayed release coating was produced which, when optimised successfully, demonstrated targeted release in volunteers. Based on analysis of recovered dosage forms, over 90% of the drug was delivered, yet

plasma levels were much lower than for rectal administration of the same dose. Additionally, imaging the dosage forms by gamma scintigraphy *in vivo*, showed that plasma levels began to rise only after the dosage form had reached the ileocecal junction or the ascending colon, regardless of any delay in time to reach that region (fed state or fasted state)⁶⁷. A potential commercial embodiment of the technology for the delivery of prednisolone metasulfobenzoate sodium is the formulation referred to as COLAL-PRED which has been the subject of human clinical trials. The concept raised some interest in its commercial potential and was licensed by the technology owner Alizyme to Norgine BV, Prometheus Laboratories and TSD Japan Inc⁶⁸. The Phase 3 trial, however, failed to meet one of the primary endpoints for efficacy and the product appears not to have been pursued further⁶⁹.

CODES

CODES represents a different approach to microflora-activated drug delivery from a coated dosage form that utilises the ability of colonic bacteria to degrade certain

polysaccharides to organic acids. The drug-containing tablet core can contain lactulose, or is coated with lactulose. The tablet is then coated with amino methacrylate copolymer (Eudragit E™), followed by a second coat of enteric polymer, methacrylic acid–methyl methacrylate copolymer (1:1), Eudragit L™ (see Figure 2). In a technology variation, a lactulose-free tablet, is coated with amino methacrylate copolymer and co-dosed with a second tablet containing lactulose coated with methacrylic acid–methyl methacrylate copolymer (1:1). The two tablets are enclosed in a methacrylic acid–methyl methacrylate copolymer (1:1)-coated capsule⁷⁰. The dosage form, therefore, is activated in the colon by dissolution of the enteric coat. Colon microflora degrade lactulose to acid metabolites in the immediate vicinity of the therapeutic agent-containing tablet and that causes breakdown of the acid-soluble amino methacrylate copolymer to liberate the contained drug from the tablet core (Figure 2).

The functionality of the technology was confirmed in an

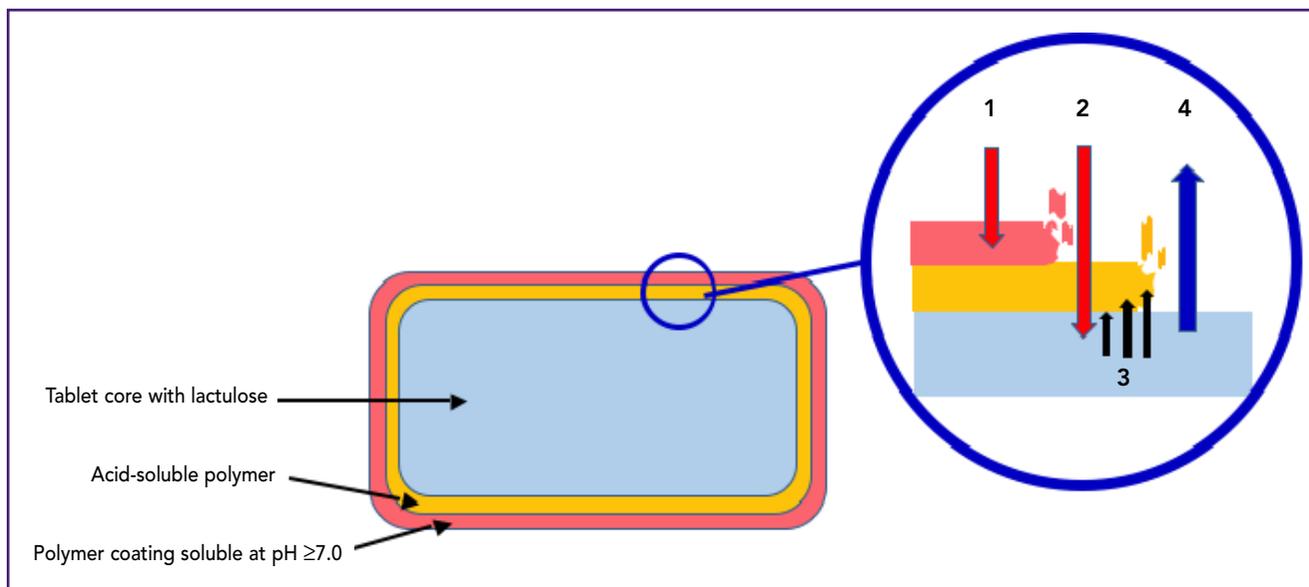


Figure 2. CODES technology. 1. Once in an environment where the pH is above the threshold for polymer dissolution (distal ileum), first coating layer dissolves exposing second layer. 2. Second layer is not soluble at pH of distal ileum and colon but allows fluid to penetrate to core. 3. Intestinal bacteria metabolise lactulose in core to acidic metabolites that cause dissolution of acid soluble coat. 4. With acid-soluble coat removed, drug is liberated from core at target site.

animal model using 5-aminosalicylic acid as the colon-targeted compound⁷¹, and the original patent claims effective delivery of insulin and salmon calcitonin to the colon⁷⁰. In a γ -scintigraphy study of the *in vivo* performance in human subjects of placebo tablets with the CODES coating technology, the radiolabel incorporated into the tablet cores was only released after the dosage form arrived in the colon and there was an induction period on arrival before the disintegration of the tablet was seen, probably associated with the time required for acid generation and dissolution of the acid-soluble amino methacrylate copolymer core tablet coating⁷². Beyond the functional demonstration with 5-aminosalicylic acid, additional applications of this technology to the delivery of small or large molecules have not been reported.

PHLORAL

PHLORAL is a hybrid pH/microflora-activated technology developed by some of the investigators who had previously developed COLAL, where it seeks to improve the consistency and accuracy of delivery, as well as assure rapid release of contained drug. COLAL relies on the controlled swelling of the amylose/ethylcellulose coating which can be a slow process resulting in a sustained-release mechanism⁷³ that is not well-suited to fast release in the colon which leads to better targeting of the whole colon. PHLORAL aims to resolve these aspects by virtue of a pH and/or microflora triggered system as a "fail safe" targeting mechanism⁷⁴. It can be manufactured using conventional pharmaceutical manufacturing equipment and is being applied to several products currently in clinical trials, including an advanced stage trial of a product for the treatment of IBD⁷⁴.

PHLORAL uses methacrylic acid-methyl methacrylate copolymer (1:2), Eudragit S™, as its

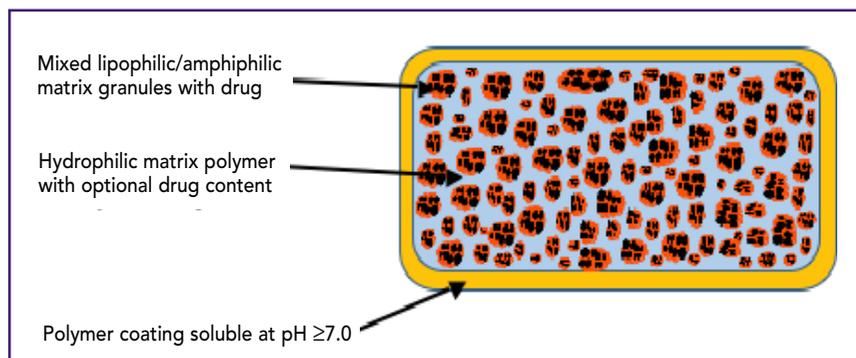


Figure 3. MMX technology. Once at or beyond the terminal ileum, the pH-dependent soluble film coat will dissolve and allow hydration of the hydrophilic polymer matrix. This may contain drug which will then release by a diffusion process. As fluid continues to penetrate the hydrating viscous hydrophilic polymer matrix it reaches the lipophilic/amphiphilic granules and allows release of drug from those, again by diffusion through the hydrated hydrophilic matrix. There are embodiments of this technology that just have lipophilic drug containing granules, rather than the mixed lipophilic/amphiphilic granules, and embodiments where the hydrophilic matrix is initially free of drug.

pH-dependent soluble polymer, which starts to dissolve at pH 7.0, and it employs amylose or amylopectin as the microflora-degraded polysaccharide. The mixed polymer/polysaccharide film around a dosage form is applied using fluid bed coating from a solution/dispersion prepared by mixing appropriate amounts of the amylose dispersion in an organic/aqueous solvent and the enteric polymer solution, to obtain a preferred polysaccharide:polymer ratio⁷⁵. The optimum pH-dependent polymer:amylose ratio was found to be 7:3, which shows excellent resistance to *in vitro* drug release at pH 1.2 and pH 6.8 (for up to 12 hours), but at pH 7.0 without enzymes or at pH 6.8 in the presence of α -amylase from *Bacillus licheniformis*, drug release is initiated at around 3 hours and is complete within 4–6 hours⁷⁵.

PHLORAL has been demonstrated as superior to purely pH-dependent polymer systems in a study in eight healthy human subjects⁷⁶. Core tablets labelled with technetium-99m (99mTc, 4MBq) were coated with the PHORAL coating and dosed in a randomised crossover protocol to the subjects either fasted or fed (after a 392 kcal breakfast), or 30

minutes prior to the breakfast. Following normal meal times, lunch 4 hours post dose and dinner 9 hours post dose, the release of the radioactive label from the dosage form was measured *in vivo* by γ -scintigraphy. In all cases (irrespective of feeding status), the label was released at the target site, either at the ileocecal junction, the ascending colon, the transverse colon or at the splenic or hepatic flexures. No dosage forms released any of the label in the stomach or small intestine and no dosage form failed to release the label *in vivo*⁷⁴. This clearly distinguishes this technology from the purely pH-dependent technologies typically used in established colon-targeted therapies where, in a number of cases, dosage units failed to release at all⁷⁷.

MMX® technology

A combined delayed-release/extended-release tablet technology for the delivery of therapeutic agents to the whole colon has been developed, clinically validated in IBD and commercialised (for the glucocorticoid budesonide and the anti-inflammatory mesalazine). The technology is described as a multi-matrix structure, hence MMX⁷⁸. Tablets consist of a dispersion of



drug-containing lipidic granules in a hydrophilic matrix coated with enteric acrylic copolymers. The coating delays the release until the tablet arrives at the intestine where the coating dissolves and the extended-release drug delivery begins. Release over the length of the colon allows for the topical application of the drug to the whole bowel surface affected by inflammation^{78,79}.

The tablet (**Figure 3**) is made by combining drug, a lipophilic matrix-forming agent (for example, stearic acid, stearic acid/carnauba wax mixture or stearic acid/beeswax mixture) and an amphiphilic agent (for example, lecithin or diethylene glycol monomethyl ether), with a binder (low viscosity hydroxypropyl-cellulose or povidone) to form granules. These granules are blended with other non-functional excipients and the hydrophilic matrix-forming excipients (for example, hydroxypropylcellulose, carbomer, alginate), and optionally additional active ingredient (dependent on dose and drug-release profile desired), and tablets are compressed from this blend. The tablets are then coated with enteric polymers, typically a mixture of methacrylic acid–methyl methacrylate copolymer (1:2) and methacrylic acid–methyl methacrylate copolymer (1:1)^{79,80}.

The innovators of this technology have successfully demonstrated the efficacy of infliximab (anti-TNF α) delivered topically (as an enema) to a very small number of human subjects as treatment for IBD, and have completed an initial demonstration of the feasibility of incorporating the monoclonal antibody into MMX technology oral dosage forms⁸¹.

SmPill (LEDDS)

Cyclosporine has been employed as therapy (principally by infusion) in IBD, notably in steroid refractory ulcerative colitis, but is associated with considerable toxicity, including seizures and fatal opportunistic infections. The availability of the oral microemulsion formulation has

allowed for oral delivery and the targeting of low circulating cyclosporine levels to manage adverse events⁸². Minimising absorption and targeting drug release in the colon might offer an improved way of using cyclosporine for the treatment of IBD.

A technology that allows the delivery of a solubilised form of a poorly water soluble drug to the colon has been applied to cyclosporine and this product has been studied in ulcerative colitis patients in Phase 2 trials with plans for Phase 3 trials advancing⁸³. The technology, SmPill ("single multiple pill") and its predecessor LEDDS ("liquid/emulsion drug delivery system"), involves the bringing together of two liquid streams as a concentric single flow, the inner stream being the drug dissolved in a suitable oil/surfactant and the outer stream being a hot gelatin/sorbitol solution. The concentric streams pass into a cooled immiscible liquid with vibration that breaks the stream into droplets yielding drug-in-solution cores with a solidified gelatin/sorbitol outer shell. The so-formed "minicapsules" are then coated with sustained release and/or enteric coating polymers. These can be ethyl cellulose or ammonio-methacrylate copolymer type B (sustained release), or a pH 7.0 soluble proprietary acrylates copolymer enteric coating (Eudragit[®] FS 30D) or mixture of ammonio-methacrylate copolymer type B and ammonio-methacrylate copolymer type A (sustained-release coating) before being coated with a pH 7.0 soluble proprietary acrylates copolymer enteric coating (Eudragit[®] FS 30D)⁸⁴. The minicapsules can be administered in several ways, e.g. incorporated into a unit dose dosage form such as filing into a hard gelatin capsule or provided as a sprinkle to add to food.

The company involved in developing SmPill cyclosporine for ulcerative colitis is also developing a SmPill formulation for the treatment of Crohn's disease.

Some thoughts on the newer therapeutic entities and the role of GI-targeted site delivery technologies

There is a significant group of new therapeutic entities being advanced for new IBD molecular targets and also new targeting delivery technologies being researched or in clinical trials. The desire for systemic delivery as opposed to local intestinal mucosa delivery remains debatable and the outcome may possibly depend on the independent molecular mechanism and its location on the epithelial cell surface, the epithelial layer, the lamina propria or submucosal tissue. However, the target product profile may change with each option and lead to changes in the therapeutic index. The example of the rectally administered, poorly absorbed ASO, cobitolimod, exemplifies the idea that local targeting can be beneficial. A key question is would targeting ASOs or other macromolecules orally, by hybrid-trigger approaches, expand their potential to both Crohn's and ulcerative colitis indications, wherein minimal systemic exposure may be attractive. Some compounds may not be more effective as targeted delivery, for example, the possible requirement for systemic exposure in the case of ozanimod and laquinimod.

Such new macromolecular entities (ASOs, peptides, proteins, monoclonal antibodies and their derivatives) face significantly greater biopharmaceutical risks to reach the desired cellular target than their small molecule counterparts. While the delivery system clearly plays a crucial role to ensure reproducible release at the right target location, the drug must remain intact and get rapidly absorbed to reach the desired cellular target location. This is not easily achievable for high molecular weight drugs, especially for targets deeper in the intestinal wall. Premature release exposes the macromolecule drug to chemical and enzymatic inactivation within minutes, as the intestinal enzymatic barrier designed to protect against



foreign macromolecular material kicks in.

Molecular modifications and formulation approaches can temporarily resist inactivation, buying additional time to allow absorption. Unnatural amino acids for peptide/protein drugs or chemically modified nucleic acids such as phosphorothioates or locked RNA/DNA are examples of molecular modifications designed to evade protease and nuclease inactivation, respectively. Additionally, formulation additives can shield the drug or temporarily reduce the activity of intestinal enzymes in the local vicinity. Hydrophobic oil-based cosolvent systems block enzyme access to solubilised drug; acidic buffers lower the micro-environmental pH temporarily reducing enzyme activity; and co-administration with enzyme inhibitors directly influence enzyme activity. Nevertheless, these new molecular entities are gaining prominence as advances in delivery technologies find ways to manage the biopharmaceutical risks to enable the development of promising new products for clinical testing.

In a snapshot review of all investigational (announced research stage and clinical stage) and approved drugs to treat IBD using a drug delivery/drug product database (Pharmacircle, August 2016), the following trends emerge: about half of all drugs in discovery/development are small molecules and the other half are novel molecular types (peptides, proteins, ASOs, siRNA, etc.). About half of all treatments listed appear to employ the oral route, the other half utilising the injectable route. For the oral route, conventional enteric coated systems that have been the primary strategy in IBD for the last couple of decades make up two-thirds of the technologies employed, while oral matrix delayed release, barrier film particulate technologies, osmotic pumps, gastric retentive systems make up the remaining third of all technologies. Surveying the clinical

progress for these technologies, about 2–3 dozen assets are in each of the three phases of clinical development, although many of the older conventional technologies with patents expired are less active or no longer being pursued. Taken together, the large number of active programs in clinical development in IBD highlight a strong medical need for innovative medicines and an active area for leveraging novel and reproducible delivery technologies to target drug to the diseased state.

The use of conventional enteric coatings may offer the most practical way to target intestinal release, but provides high risk of variability in the site of delivery due to premature release or lack of release of drug⁸⁵. PHLORAL, COLAL, CODES and MMX are examples that represent proven delivery technologies for which pH and/or microflora trigger more or less consistent release of drug in the human distal intestine/colon. However, the diseased-state can pose many delivery hurdles: profuse bleeding, perforation of the bowel or obstruction can lead to a dynamic GI lumen that may not be consistent from patient to patient. Infections induced by luminal bacteria, scar tissue and growths can form strictures that can impede progress or delivery of drug, and there can be significant variability in small intestine transit time in IBD patients relative to healthy subjects which may confound consistent colonic delivery of exposure time-triggered delivery systems^{6,63}. Even in healthy subjects, high variability with colon-specific polymers has been reported.

An examination of the interplay of dosage form disintegration time with pH, and intestinal transit in the fasted and fed state indicate that dosage forms formulated with the pH-dependent polymer methacrylic acid–methyl methacrylate copolymer (1:2) may not consistently release drug and may remain intact. In the fed state, this is further exacerbated⁷⁷. It will be of

no surprise that one or more of these delivery technologies is at some near-term stage combined with one of the newer therapeutic entities (either one of those mentioned in this article or one that is yet to emerge into human trials) to provide a much-enhanced therapeutic option for the treatment of IBD and specifically ulcerative colitis.

Additionally, there are several other novel strategies described recently that attempt to reduce GI transit-based variations and pH variations to improve drug delivery. These include: (a) vesicular or emulsion based systems, (b) mucoadhesive or gelling polymer-based systems, or (c) compression-coated oral solid dosage form systems⁶.

Vesicular- or emulsion-based systems are comprised of small droplet-like structures of phospholipids, surfactant and drug that may be delivered in the solution state or solid state and the SmPill technology, as a pre-solubilised drug formulation, solid mini-sphere or gel-like particles coated with enteric polymers, may be considered in this class. Solid lipid nanoparticles are also gaining interest, especially for ASOs and siRNAs, as, employing cationic lipid/neutral lipid/cholesterol formulations, they may be able to neutralise the charge associated with nucleic acids protecting the RNA/DNA against degradation, and facilitate intestinal mucosa permeability as nanostructures⁸⁶.

Mucoadhesive polymer-based systems with drug in modified hydrogel polymer matrix, poly-lactic/poly-glycolide, or methacrylate-based polymers as particulate systems may deliver contents over a prolonged duration to the inflamed intestine. A hyaluronan drug delivery technology using hyaluronic acid to improve mucoadhesion to provide improved localisation of drug at the site of intestinal lesions, although relying on enteric coating for targeting is in Phase 2 trials⁸⁷.

Compression coated



technologies like GeoClock employ compression wax coating over a tablet core (potentially with specific geometry) to release after a specific period of time regardless of motility, pH and food. A predisoned product, Rayos/Lodotra[®] based on Geoclock[™] technology, results in a C_{max} at 6 hours compared to the immediate-release formulation providing the opportunity for chronopharmacokinetic profile overnight⁸⁸. However, as this is a time-based drug release technology, reliable, consistent delivery into the colon may be challenging; this technology is maybe better suited to small intestinal delivery and so might be an option for delivering one of the novel, emerging therapeutic entities treating Crohn's disease, especially when this is limited to the lower small intestine.

Conclusion

This review describes some of the therapeutic agents, drug delivery strategies and drug product strategies being considered for the treatment of IBD. Small molecules and the emerging new macromolecular types require a robust means to target drug precisely to the inflamed GI tissue. The physiological variables of the disease state have profound implication on the drug delivery system. They render many of the traditional modified-release technology approaches through pH or time-triggered methods perhaps insufficiently reliable and of variable effectiveness in targeting the inflamed intestine. Small molecules and macromolecules have different biopharmaceutic requirements for ensuring stability and deliverability at the target site which needs to be considered in determining a delivery technology. Many novel delivery technologies that could be geared towards these molecular types have become available and may have potential in not only improving delivery, but improving the safety profile and local efficacy profile of drug products too.

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REGENERATIVE MEDICINE: ENERGISING TECHNOLOGY EVOLUTION TOWARDS FUTURE MEDICINE

by Cecilia Van Cauwenberghe and Sudeep Basu

Although still demanding more specialisation for both scientists and clinicians, regenerative medicine is destined to address the most concerning challenges of current medical therapies.

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Focus area 1: Technology synergy

What are the most prospective technologies empowering regenerative medicine?

Developments in stem cell technology and tissue engineering combine advanced biomaterials with small molecules and biologics to replace or regenerate human tissues and organs and restore their functions. Regenerative medical approaches represent perhaps the most valuable technological synergies that have emerged. Some key innovations in the regenerative medicine space proving this remarkable technology synergy are described in the **Table 1**.

Lewis *et al.*¹ illustrate such synergy among stem cell research, three-dimensional (3D) bioprinting and nanobiosensing. Adjacent technologies such as 3D bioprinting have been used to shape 3D spheroid cultures. Provided with magnetic nanoparticles, these cultures are grown emulating original environment, keeping the cells undifferentiated over long periods before being placed into the desired tissue ecosystem. They are then activated to migrate towards the injured tissue and begin to differentiate.

Among different types of

nanomaterials, Graphene has proven to be biocompatible and conducive scaffolds for stem cells. Menaa *et al.*² highlight the role of this two-dimensional nanomaterial in biomedical research owing to its intrinsic properties. Notable advantages include promoting stem cell adhesion, growth, expansion and differentiation, without affecting cell viability.

Why induced pluripotent stem cells (iPSCs) are in the spotlight

Pluripotent stem cells can potentially differentiate themselves to produce any cell or tissue. In 2006, Yamanaka *et al.* demonstrated that pluripotency could be induced in adult cells using just four embryonic transcription factors. Since then, more than 5400 papers related to iPSCs have been published worldwide³, depicting progress in the field⁴. Following academic trends, the development of cell-based medicines using iPSCs became one of the main goals targeted by companies working in the field of regenerative medicine.

There are several advantages to iPSCs over pluripotent stem cells. Directly generated from patient somatic cells, the utilisation of iPSCs do not involve the destruction of preimplantation stage embryos,

thereby circumventing ethical issues of pre-existing embryonic stem cells technologies. In addition, this enables iPSC technologies to create patient-matched pluripotent stem cells avoiding immune rejection after transplantation. Based on these facts, in the long-term, the impact of iPSCs is expected to significantly drive the global market for advanced stem cell therapeutics.

An excellent discussion covering applications, challenges and future perspectives of human iPSCs⁵ elucidated how iPSC technology has evolved. Several recently published articles chronicle the developments, including the development and characterisation of scaffold-free 3D spheroid models of iPSC-derived human cardiomyocytes⁶; and the use of extracellular vesicles responsible for mesenchymal stem cell-induced effects under physiological and pathological conditions to improve post-stroke neuro-regeneration and prevent post-ischaemic immunosuppression⁷, among others.

However, Yoshihara *et al.*⁸ cite genomics instability and genetic variations in iPSCs as a tangible risk factor for adverse effects, including malignant consequences. The researchers emphasise the critical need for an in-depth understanding of the origin and functional outcomes of such genetic mutations for the successful advancement of iPSC-based therapies.

Focus area 2: Clinical translation

What would be the best perspectives to address current challenges in regenerative medicine?

Although clinical translation faces some challenges, novel technologies addressing cell reprogramming are dramatically reshaping the field. In parallel, the development of new genome scanning technologies and products to detect genome instability is growing rapidly. Novel methods to identify genomic aberrations, copy number variations and single-nucleotide polymorphisms are propelling the genome sequencing market, which is expected to exceed



Table 1: Key Innovations in the regenerative medicine sphere reflecting technology synergy approaches

Innovation	Brief description	Therapeutic areas	Industry players
Autologous cells generation for transplantation	Autologous cells, potentially injected directly into damaged regions of the organ or used in regenerative tissue patches, have the advantage of avoiding rejection and, hence, costly immunosuppressive regimens	<ul style="list-style-type: none"> Diabetes mellitus, through bone marrow stem cell transplantation or microencapsulated islet cells using novel biomaterials Heart muscle regeneration after myocardial infarction and cardiomyopathy Tissue-engineered skin substitutes using autologous stem or progenitor cells used in skin loss conditions, such as burns, wounds and diabetic ulcers 	e.g. co.don AG; ZioPharm; Lonza; Miltenyi Biotec; TotipotentRX; Cytomatrix; TransTissue; NantKwest
Human oligodendrocyte progenitor cells transplantation	Treatments based on transplants of human oligodendrocyte progenitor cells have demonstrated the potential to replace or remodel nerves, and even myelin, and, eventually, contribute to axonal regeneration in traumatic injuries	<ul style="list-style-type: none"> Parkinson's disease Alzheimer disease Neuroscience 	e.g. Asterias Biotherapeutics; Cartherics
Monoclonal antibodies enlistment to slow/ reverse senescence	Regenerative medicine approaches are not focused solely on repairing or replacing tissues and organs, but also on slowing or reversing biological processes related to aging or degenerative damage	<ul style="list-style-type: none"> Multiple sclerosis Cancer immunity Autoimmune disease Rare and genetic diseases 	e.g. SIWA Corporation; Abnova
3D bioprinting for use in drug discovery and medical research	3D bioprinting ultimate goal is the printing of tissues and cells to develop entire human organs, expecting to have the greatest impact in life sciences by allowing the design and creation of tissues for drug discovery and medical research	<ul style="list-style-type: none"> Eye diseases Cartilage, skin, and bone regeneration 	e.g. Organovo; BioBots; Cyfuse Biomedical; Aspect Biosystems; 3D Bioprinting Solutions; Rokit

\$20 billion by 2020 at a compound annual rate of 10%.

Rosenthal and Badylak⁹ associate the challenges and opportunities for regenerative medicine applications based on three leading research trends aiming to uncover new personalised and precision intervention using regenerative medicine approaches. First, an assessment of the molecular heterogeneity of patient immune responses to provide vital clues to the progression of disease and prompt design of personalised therapies. Second, a multi-disciplinary environment for the clinical delivery of regenerative therapies that engage clinical research centres with a broad focus on regenerative medicine. Crucial for the safe delivery of exogenous cells, such centres should entail a substantial degree of infrastructure in terms of cell growth, advanced biomaterials, high-resolution clinical imaging and access to clinical trials compliant facilities. Third, functional

imaging advances to assess tissue improvement, and complementing metabolic signatures, along with precision medical approaches to scan individual genetic variations.

How clinical translation is being advanced worldwide beyond stem cells

During the past decade, a number of therapies have received US Food and Drug Administration clearance or approval and are commercially available, demonstrating generally successful results. The commercialisation milestones achieved have been reviewed^{10,11}. However, the promise of regenerative medicine must translate clinically for measurable progress to be achieved. With this objective, in 2014, several initiatives focused on new pathways for regulatory approval were initiated.

The introduction of the Early Approval System (EAS) in the Japanese regulation, including its condition of post-market

surveillance, has revolutionised the industry, remarkably impacting therapeutics cycle development. Japan is presently in the spotlight, significantly attracting business in the field. Under the new regulation, companies will be able to perform clinical research more cost- and time-effectively in Japan, enabling the reduction of the full cost of each therapeutic product discovery and development by 50% with the introduction of the EAS. The safety standards call for testing iPSC for signs that they may turn cancerous. As a pilot proof, the Kansai area will also introduce EAS in the field of medical devices. Under the scheme of the Safety Act for Regenerative Medicine, medical institutions are allowed to outsource cell development and processing operations to external organisations. The normative has also impacted the research funding scheme, which demanded the establishment of an Independent Administrative Agency of the Japan Agency for Medical



Research and Development (AMED), and highly organised safety and quality standards are needed in addition to post-market surveillance. In a recent report by Frost & Sullivan¹², principal industry interaction strategies depicting the key players across industries in Japan are illustrated, listing the principal foreign companies targeting Japan, as well as the Japanese companies awaiting opportunities in the space of regenerative medicine.

Similarly, in the US, the Georgia Research Alliance and the Georgia Institute of Technology are propelling the National Cell Manufacturing Consortium, an industry-academic-government partnership responsible for the National Roadmap for Advanced Cell Manufacturing, sponsored by the National Institute of Standards and Technology (NIST). In Europe, the TERMIS-Europe Industry Committee intended to address the two main critical issues in the clinical/commercial translation of advanced therapeutic medicinal

products by propelling entrepreneurial expansion of disruptive innovations, and discussing new pathways for regulatory market approval.

How companies are competing to leverage the optimal niche

In the competitive landscape across regenerative medicine, Fujifilm Corporation represents a paramount instance of technology synergy and business strategy. Through the consolidation of the group after the acquisitions of CDI and J-TEC, Fujifilm is focused on expanding regenerative medicine product line by combining its proprietary extracellular matrix with somatic and stem cells products from JTE; regenerating organs via iPSCs; and expanding drug discovery support by conjugating extracellular matrix where iPSCs can grow and differentiate for clinical trials. Osiris Therapeutics has advanced stem cell technology to exploit the natural abilities of cellular matrices to promote the

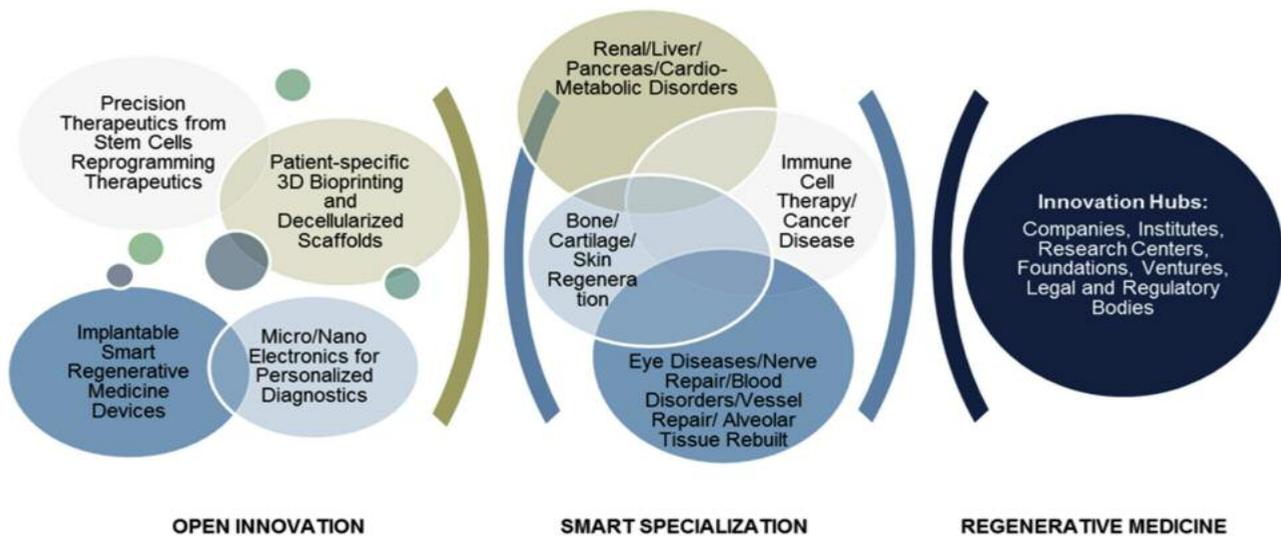
body's natural healing through the MSC Primer platform, receiving approval for remestemcel-L in Canada and New Zealand for the treatment of graft-versus-host cell disease, the first approved stem cell drug. After granting two patents from the Japanese Patent Office addressing 3D methods for expanding placental and adipose cells, Pluristem has partnered with a venture company derived from the University of Tokyo to advance the treatment of ischaemic diseases. Focused on large degenerative disease markets, BioTime expects to reach a broader market facing multiple near-term clinical milestones worldwide.

Conclusion

Why focus on regenerative medicine?

In the coming years, regenerative medicine is expected to experience a great revolution in terms of products launched and customer niches penetrated. Timelines and costs associated with the

Regenerative Medicine: Innovation Model, Global, 2016

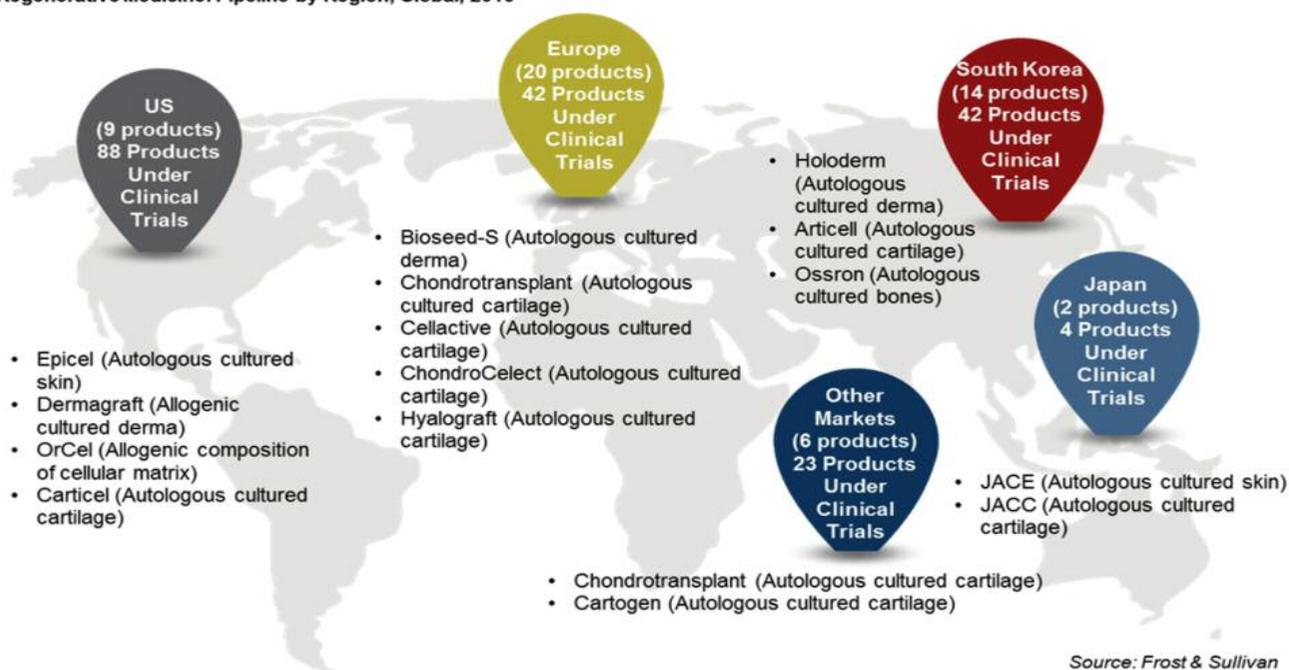


Source: Frost & Sullivan

Figure 1. Focus area 1: Technology synergy – how to propel research and development activities towards future medicine.



Regenerative Medicine: Pipeline by Region, Global, 2016



Source: Frost & Sullivan

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Figure 2. Focus area 2: Clinical translation – how to advance novel solutions to address the most concerning medical needs.

development of novel solutions will be critical factors impacting the evolution of the field over the next 5–10 years. A master approach focused on how companies can propel research and development activities to better compete to leverage the optimal niche is depicted in **Figure 1**. Regarding regional approaches and therapeutic focus, **Figure 2** illustrates presently marketed products and ongoing clinical trials by region.

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HOW A STUDENT ASSOCIATION PREPARES ITS MEMBERS FOR THE PROFESSIONAL WORLD

by Clara Brandt

In this article, you will get to know EPSA, the European Pharmaceutical Students' Association, and its projects closer. The article will mainly focus on the projects EPSA carries out in collaboration with the European Industrial Pharmacist Group (EIPG), such as Mentoring Project and Chat with Professionals. We believe these two projects have a great impact in shaping student's professional path by providing them insight in diverse pharmaceutical areas as well as the skills and valences needed.

Clara Brandt started studying pharmacy in 2011 at the Christian-Albrechts University, Kiel, Germany. Soon, she discovered her interest in extracurricular activities which led to her becoming board member of her local student association, member of the university's senate and, in 2015, part of the EPSA team, where she currently holds the position of Professional Affairs Coordinator.

During their academic years, students feel the need to learn and acquire valences that are not taught in their programme of studies. They want to be distinguished from other students for their capacities and qualities rather than their scientific background. Students believe those qualities will make a difference when choosing their career field. The blurry picture students have once they finish their degree is also a reality: it is a big challenge to define which career to pursue. EPSA provides students not only with tools to enhance their professional development but also with insights in different pharmaceutical fields.

EPSA is a non-profit, non-political organisation representing 160,000 pharmacy students from 35 countries across Europe in 43 national and/or local organisations. EPSA exists to develop the interests and opinions of European pharmacy students and to encourage contact and cooperation between them by



increasing student mobility.

But what does EPSA do exactly and how do they gain the knowledge to help fellow students?

First of all, EPSA believes that providing direct contact between students and professionals is the most effective and, therefore, efficient way for students to learn about any career path and to clarify all the questions related to it. To meet this vision, EPSA organises Chat with Professionals which is focused on online learning where professionals enlighten students about their field of work during an approximately 2-hour period. During one year, there are four editions of Chat with Professionals, usually in close collaboration with EPSA's partner EIPG. Every edition focuses on one pharmaceutical field depending on student's interests.

EPSA feels that after students finish their degrees, the knowledge

of recent graduates about the role that we as pharmacists have in industry is very little. Consequently, the topics that mostly attract our audience are very much industry related. The most recent editions of Chat with Professionals tackled three different topics related to industry, namely quality assurance, regulatory affairs, and marketing. Once the topic is chosen, EPSA arranges speakers who can provide students with their experiences, and information on the background and skills needed for the respective position, and describe their everyday work life.

EPSA aims to ensure that European pharmacy students start their professional journeys equipped with the knowledge and skills that correspond to the needs of modern healthcare. That is why we strive to have a dynamic presentation where students can clarify any questions they might have with the speaker and get to know which skills to develop before entering the work market. Normally we have around 100 participants per edition, thus we can conclude that there is great interest among students and the previous editions have been quite successful.

In order to carry out this project and to provide students with the most qualified professionals, EPSA is collaborating with professional partner associations, such as the EIPG, who help us find professionals from respective fields who are willing to devote their time and energy to develop students and broaden their horizons.

Once a student has discovered which field seems interesting for him, he might want to dive even deeper into the field and to provide him with this opportunity, also in collaboration with the EIPG, EPSA grants the chance for students to establish close contact with professionals through the Mentoring Project.

The EPSA Mentoring Project - a chance to learn directly from professionals

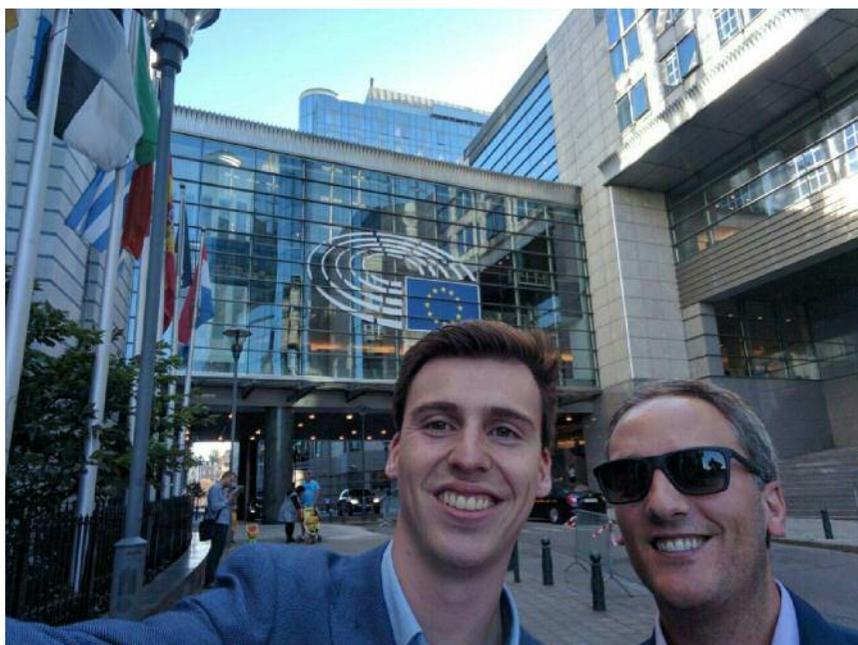
The Mentoring Project is one of EPSA's youngest projects, aiming to group interested students with



professionals working in different areas. The main goal of this project is to enlighten students about working in the area of their interest and to give them guidance on how to pursue their career and achieve their goals. EPSA is responsible for finding the appropriate mentors within their network and always strive to have a very diverse pool of mentors so they can meet the needs of all interested students.

In order for this project to be successful, it is necessary that both parties (mentors and mentees) are fully committed and that a good dynamic between them exists. Not only mentees benefit from this project, mentors also gain new experiences and have the opportunity to contribute to the professional development of students. The mentoring phase lasts 6 months and mentors and mentees usually meet online, but, when possible, they are encouraged to meet in person in order to strengthen the bonds. During these meetings, goals are set and the mentor helps the mentee to find the correct pathway in order to start the desired career. Not only does the mentor provide the mentee with useful tips but he also clarifies his everyday life and working routines, and the required skills and interests for the respective career area.

Marta Simoes, a participant of the project says: "Being in my fourth year of studies of pharmaceutical sciences, I felt it was time for a different approach in my degree. Thus, I decided to apply for the EPSA Mentoring Project in regulatory affairs. From the very beginning, my mentor warned me he would not be my teacher, meaning that he would always be available to answer all my questions but I would have to research for myself. For me, that was the main essence of the project: I was developing myself with guidance from someone who was quite experienced. Hence, during those 6 months, I came to understand what is expected of someone working in that area and I took advice for future options that could lead me to a path



in regulatory affairs. I definitely recommend this project to everyone and, if you want to gain the greatest profit from it, keep doing your homework even without a teacher."

This project is definitely very enriching for mentors as well, as Rita Machado confirms while talking about her personal experience. "This year began for me with a fresh new challenge: being a mentor in the EPSA project. And I can tell you it was a great experience! I connected with my mentee in January, and since then we have met on a regular basis. We were both very enthusiastic and interested about the programme, and we have shared scientific knowledge, personal experiences and perspectives. It was certainly an enriching experience for both, and especially an apprenticeship for me. Although my mentee was only in the second year of pharmaceutical sciences, and I was guiding her in the research and development field, I was able to show her my work and give her a greater perception of working in a lab. Being a mentor provided me with a great opportunity to participate in someone's academic path and possibly making a positive impact on it. I hope my experience was valuable for Aleša Bricelj!"

EPSA fosters the continuous improvement of its projects and so

the input and feedback from participants are highly valuable. After each mentoring phase, feedback is collected from mentors and mentees to develop the project and to enable EPSA to meet even more needs of both mentors and mentees the next time and guarantee the best outcomes are achieved.

As the mentees should also develop themselves personally, the project is accompanied by a side educational programme including mainly soft skills trainings. EPSA wants to bring these soft skills to a wider range of students, because they are trying to be the bridge between students from university and the professional world. They are aiming to prepare their members for professional life in addition to the bare scientific knowledge gained from their degree, achieved with the EPSA Training Project.

The EPSA Training Project

At the core of every company, there are people working together towards common objectives. If we talk about the pharmaceutical industry, it is somewhat very likely to find pharmacists amongst the teams. To be able to work in such a competitive environment, the pharmacist needs to be much more than the medicines specialist – he or

she also needs to be a people specialist. The skills needed to be able to work within a team, to be able to withstand adversity, to be able to think differently or critically or even to be able to manage a project or team, are known as soft skills. In EPSA, we believe soft skills are an important part of students' development and they are fundamental for pharmacy students' professional success.

Even though the importance of these skills is widely acknowledged, there is an imminent lack of reliable sources of this knowledge. This is why EPSA decided to provide soft skills training sessions to pharmacy students all over Europe. During this training, students are invited to share their experiences, while they are provided with the tools and knowledge to improve in a particular skill or set of skills. Every training session is, therefore, unique, and participants are challenged in different ways to make significant changes in their lives. Pharmacy students can then change their habits, including properly manage time and stress, combat the fear of talking in public, understand and carry out all stages of a project, work in a team overcoming conflicts and dealing with different personality types and provide structured and valuable feedback.

To provide quality soft skills training to pharmacy students in Europe, EPSA created the EPSA Training Project back in 2009. One key part of this project is the EPSA Trainers, a group of around 60 dedicated students that devote

countless hours to learn more about soft skills and how they can teach them to other students in carefully designed training sessions. EPSA Training Project is comprised of different activities that aim to bring soft skills to as many students as possible and ultimately to see these soft skills included in pharmacy curricula.



Apart from learning, working experience is of high value to become a better professional once entering the job market. In order to gain this experience, EPSA believes in internships, and thus have a project which solely focuses on internships abroad for their students.

The Individual Mobility Project - how EPSA actively assures student mobility

EPSA is a great platform for students to gain more knowledge

about the pharmaceutical world and to, amongst such a variety of career paths, choose the most suitable for them. At the moment, the student has the knowledge and all the educational background, but he still needs to gain working experience in order to put in practice everything he learned through his degree and EPSA. EPSA's core mission is still to increase mobility while providing students with valuable experiences for their continuous development. To meet this value and remain the bridge between students and professionals, the Individual Mobility Project (IMP) allows students to gain work experience and to get to know a new culture.

IMP is the flagship project of EPSA, which encourages young professionals to build up international careers, and share and gain experience, thus improving the quality of pharmaceutical services in Europe. This project aims to provide their students with an experience abroad in one of the pharmaceutical fields (industry, hospital pharmacy, academy and others) for up to 12 months. During this period, the intern will gain multiple skills which will boost his employability, enhance his personal and professional background and provide him with a lifetime of experience.

If you are interested in getting to know EPSA better or in being part of one of their projects, please check the website www.epsa-online.org where you can also find the contact details of each EPSA team member!

Visit the website: www.industrialpharmacy.eu for PharmaTV and Quality by Design videos, Regulatory Review, Financial Pharma News and other current items concerning Industrial Pharmacy

www.industrialpharmacy.eu

regulatory review

The current review period has seen a number of changes in the regulation of medicines and regulatory guidance in the EU, International markets and the USA

USA

Insanitary conditions at compounding facilities

Since the 2012 fungal meningitis outbreak, the US Food and Drug Administration (FDA) has identified insanitary conditions at many of the compounding facilities that it has inspected. Numerous compounding facilities have voluntarily recalled drug products intended to be sterile and temporarily or permanently ceased sterile operations as a result of those findings.

However, the FDA does not inspect the vast majority of compounding facilities in the USA because such facilities do not register with the FDA unless they elect to become outsourcing facilities. Compounding facilities not registered with the FDA as outsourcing facilities are primarily overseen by the individual States and are not routinely inspected by the FDA.

The FDA encourages State regulatory agencies to assess during inspections whether compounding facilities that they oversee engage in poor practices and, if so, to take action, as appropriate, consistent with State laws and regulations, and also to contact the FDA.

The FDA has issued guidance to assist compounding facilities and State regulatory agencies in understanding some examples of what the FDA considers to be insanitary conditions that could cause a drug to become contaminated or rendered injurious to health, so that they can implement appropriate corrective actions.

Change in hard gelatin capsule shell supplier

When an applicant changes the supplier of a hard gelatin capsule shell, with no change in capsule composition or appearance, the information should be submitted in an annual report. However, any change in capsule composition or appearance, including change in size, colour or dye, or a change from gelatin to non-gelatin alternative, should be categorised as a prior approval supplement.

Europe

Data integrity questions and answers

The European Medicines Agency (EMA) has published 23 questions and answers (Q&As) on the topic of data integrity.

Q&A on production of water for injections by non-distillation methods - reverse osmosis biofilms and control strategies

Monograph 169 of the European Pharmacopoeia has been revised to include reverse osmosis coupled with suitable techniques for the production of water for injections.

This consultative set of Q&A is intended to provide preliminary guidance until such time as the ongoing revision of Annex I of the EU Guidelines to Good Manufacturing Practice is complete.

First comprehensive overview of global initiatives on medicine regulation

The EMA has published an overview of existing international regulatory initiatives for human medicines on behalf of the International Coalition of Medicines Regulatory Authorities.

The report lists all international projects and provides international regulatory agencies with comprehensive details on the number and scope of global initiatives that can support decision-making regarding future engagement, prioritisation and

coordination.

The aim was to raise awareness of ongoing international regulatory activities, establish a basis for a more strategic coordination, avoid duplication of efforts and identify possible gaps.

EU Guidelines to Good Manufacturing Practice Responses to the public consultation on revised Annex 17 - Real Time Release Testing

The Commission has now published the 12 responses that it received.

Medicines and Healthcare Products Regulatory Agency (MHRA)

MHRA undergoes an external inspection

The audit/inspection was conducted by a team consisting of senior inspectors from Finland, France and Spain. It was also observed (under the Mutual Reliance Initiative looking to establish equivalence between Europe and US) by the US FDA whose focus was on the Joint Audit Programme process itself rather than good manufacturing practice (GMP) systems within the MHRA.

The two main drivers for the process are to verify equivalence and consistency of the implementation of European legislation and the practical application of GMP standards by national inspection agencies across the European Economic Area (EEA) and also to preserve confidence in the equivalence of EEA GMP systems to all member states and to EU Mutual Recognition Agreement (MRA) partner countries.

The evaluation checklists adopted for the inspection were borne out of the MRA with Health Canada, and these have been adopted by both Heads of Medicines Agencies' Joint Audit Programme and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) audit programme.

(Probably quite timely and good to have in place, particularly in the light of Brexit! – MH.)



International

PIC/S PIC/S Inspectorates' Academy (PIA) is up and running

The PIA is a PIC/S initiative to set up a web-based educational centre which aims at harmonising and standardising GMP training at an international level through a

certified qualification system. PIA delivers general or advanced training and serves as a platform for discussion and sharing among regulators. It offers a single point of access to all PIC/S training activities and is being implemented in various stages. Stage 1 of the PIA will be accessible to all PIC/S Inspectorates only.

For further information on these and other topics, we suggest you refer to the websites of relevant regulatory bodies and to current and past editions of "GMP Review News" published by Euromed Communications. To subscribe to this monthly news service contact info@euromedcommunications.com

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Please contact the Managing Editor, Sue Briggs (suze.briggs@sky.com) for further information or submissions.



bottled brown

Strain 121

Do the autoclaves in your company work? They do, I hear you retort. I suggest they may not.

Join me in a voyage of imagination. We are in the bathyscaphe *Alvin*. We are 2 miles beneath the sea in the abysmal dark where tectonic plates join. Our lights illuminate a chimney of iron sulphide: a "black smoker". Scalding water plumes out. Teaming within are extremophile microorganisms. One is "Strain 121" (*Geogemma barossii*). That hyperthermophile archaean can reproduce at 121°C. Presumably, it would feel cosy at that reputedly "sterilising" temperature in an autoclave for 15 minutes. Admittedly, it is unlikely to be pathogenic to mammalian tissue at about 37°C. That is too chilly for survival and our immune stem should destroy any surviving adventurers.

Opportunities

Extremophiles might seem a threat to your pharmaceutical endeavour, but they could be an opportunity. Those organisms might be a treasure chest of new drugs. A company mining minerals from the abysmal depths might provide samples for screening. Checking various biosecurity issues connected with exotic microbes in a densely populated location might first be prudent. However, your investigations into extremophiles might hit the jackpot. For example, the radiation-loving bacterium *Deinococcus radiodurans* can repair

damaged single- and double-stranded DNA. That may interest researchers into cancer, Alzheimer's or the aging process.

Study extremophiles directly, through the spectacles of your specialty. Alternatively, view any discovery as some sort of *hint* (model, shadow or palimpsest) about a medical goal. That just may mine pharmaceutical gold. One taken-for-granted goal of medicine use is extending life. Yuval Noah Harari (English translation 2014) in *Sapiens A Brief History of Humankind* laid bare a grander goal. It is immortality: the Gilgamesh project. Gilgamesh is a Mesopotamian tale about death being humankind's inevitable destiny. However, some now think that "eternal" life is nearly within reach. Bar accidents, people would live forever.

Clearly, there could be all manner of moral and practical objections. For example, John Wyndham (1960) in his science fiction novel *Trouble with Lichen* speculated about hugely retarding the aging process. I suspect that a medicine conferring healthy immortality would be, at least, the elephant of pharmaceutical blockbusters. It would make all previous ones seem like fleas. Resveratrol-inspired compounds are one example of candidate drugs. The Palo Alto Longevity Prize will first be awarded for restoring vitality and extending lifespan in mice by 50%.

Unique abilities

This article has told you stories of

black smokers in the ocean deeps, radiophilic extremophiles and immortal humans. Another thought, borrowed from Harari, fascinates me. Suppose others would also like something to happen and agree to cooperate. That something presently exists only in human imagination. That idea Harari calls an "intersubjective reality". It may have physical manifestations.

Examples are a limited company (such as pharmaceutical). It has factories, laboratories, products and staff. But if a judge dissolves the company or it suffers a takeover, it ceases to exist, *instantly*. Another is money. It only exists while you trust that others believe in it. Humans make it exist. Money not really existing shocked me. Dare I mention quantitative easing? One industrial pharmaceutical idea is the discovery of a mega-blockbuster drug.

To Harari, ideas mean life or death. Once *Homo sapiens* existed with other, competing, species of *Homo*. One was *Homo neanderthalensis*. They were physically stronger with bigger brains. *Homo sapiens'* unique ability to believe in, and cooperate about, abstract ideas was essential to prevail. All other *Homo* species are now extinct.

So, while you with human prowess create your corporate mission statement, draft your plan or design an experiment, reflect. You are unleashing formidable weapons.

Malcolm E Brown



news from the EIPG

Medicines Shortages

As part of its participation in COST action CA15105 (European Medicines Shortages Research Network – addressing supply problems to patients), EIPG would like to encourage anyone who is aware of young researchers (defined as up to 8 years after registration) working in the area of medicines shortages to contact EIPG Executive Director Jane Nicholson (jane@nicholj.plus.com)

European Medicines Agency (EMA)

A report on the Unique Identifier and Quality Systems in the Pharmaceutical Supply Chain was presented by EIPG President Claude Farrugia at the November Interested Parties Meeting at the EMA. This included recommendations from the EIPG Statement on the update of Annex 16 on the qualified persons guidance in respect of the Delegated Regulation and a call for review of the good distribution practice guidelines to determine the responsibilities and guidance for responsible persons in respect

of the Delegated Regulation.

EIPG comments on the draft document on questions and answers on the production of water for injections by non-distillation methods have also been submitted to the EMA.

EIPG webinars for members

In collaboration with the Irish Association (PIER) and University College Cork, successful webinars have been run in October and November. The first was on the new Clinical Trials Regulation and presented by Evgenia Mengou (EV Pharma Solutions) and the second on Adaptive Pathways in Medicines Licensing by Dairine Dempsey (ICON).

There were 150 registrants for the first and 94 for the second; the vast majority of participants to date have been from Britain, Ireland and Spain. Results of the post-webinar surveys have proposed a wide range of future topics. The next webinar will be organised in early 2017 and will be on aspects of the Falsified Medicines Directive and the unique identifier.

European Pharmacy Students' Association (EPSA)

EIPG Vice-President Anni Svala described her career pathway to EPSA members in a "Chat with Professionals" webinar. Discussions have been held with members of EPSA regarding extending their Individual Mobility Project and a communication package will be prepared for distribution to EIPG Member Associations and to European Federation of Pharmaceutical Industries and Associations companies.

Bureau meeting

A meeting of the EIPG Bureau is scheduled to be held on the 21 January 2017. Nominations by Full Members for the awards of EIPG Fellow and EIPG Emerging Industrial Pharmacist should be submitted by the 1 January to Jane Nicholson, Executive Director EIPG (jane@nicholj.plus.com); the criteria for the awards can be viewed on the EIPG website at <http://eipg.eu/eipg-awards>.

Jane Nicholson, Executive Director
jane@nicholj.plus.com

PharmacoVigilanceReview



Journal on drug safety issues

Editor – Rob Begnett

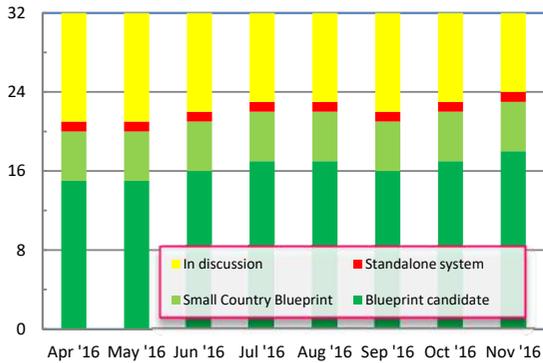
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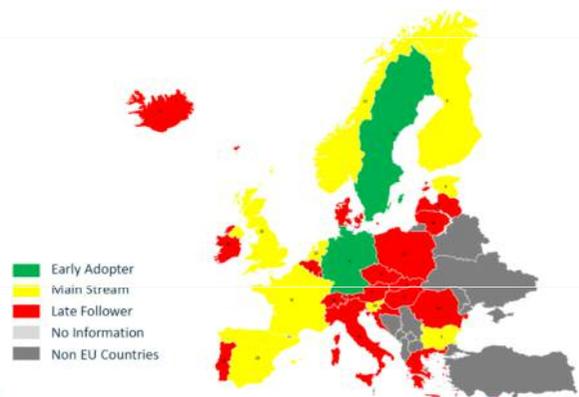
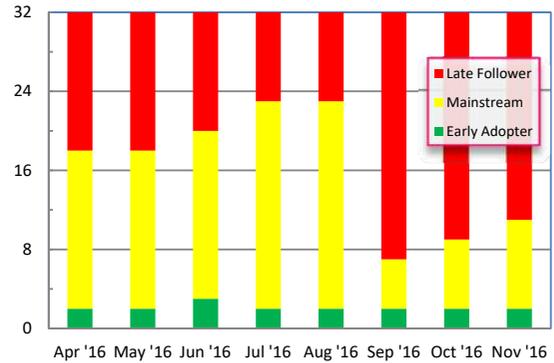
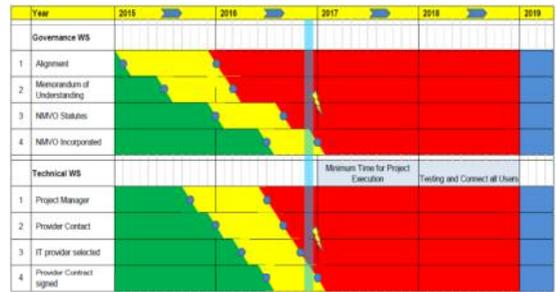
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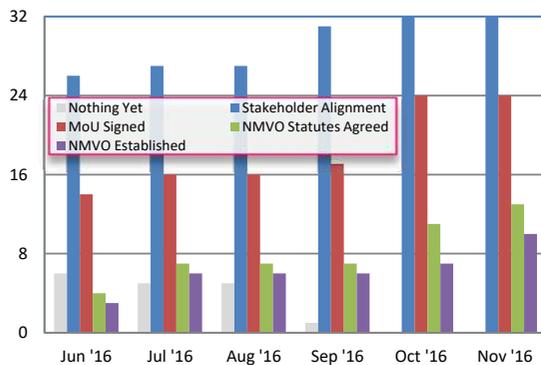
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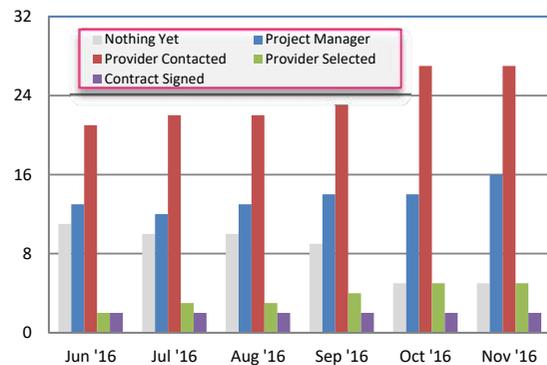
Country Readiness



Governance Workstream



Technical Workstream



events

JANUARY 2017

18–19 January 2017 – London, UK
Pharmaceutical Microbiology 2017
www.pharma-microbiology.com

23–25 January 2017 – London, UK
7th Annual Clinical Trial Supply Europe
www.clinicalsupplyeurope.com

24–25 January 2017 – Alexandria, VA, USA
12th Biosimilars Summit
www.cbinet.com

25–27 January 2017 – Amsterdam, The Netherlands
7th Annual Pharmacovigilance and Risk Management Strategies
<http://pharma.flemingeurope.com/>

30 January–1 February 2017 – London, UK
Festival of Genomics
www.festivalofgenomicslondon.com

30 January–2 February 2017 – Frankfurt, Germany
6th Annual Cool Chain Temperature Controlled Logistics Europe
www.coolchaineurope.com

FEBRUARY

7–8 February 2017 – Barcelona, Spain
World Affordable Medicines Congress 2017
www.healthnetworkcommunications.com

9 February 2017 – London, UK
Dissolution testing: current and future considerations
www.jpag.org

14–15 February 2017 – Porto, Portugal
PDA Europe Pharmaceutical Microbiology
www.pda.org

20–22 February 2017 – Berlin, Germany
7th Annual World ADC 2017
<http://worldadc-europe.com/>

21–22 February 2017 – Manchester, UK
12th Annual Biomarkers Congress
www.biomarkers-congress.com

21–22 February 2017 – Munich, Germany
Software Design for Medical Devices Europe
www.sdmdeurope.iqpc.co.uk

22–23 February 2017 – London, UK
Pharma Pricing and Market Access Europe 2017
www.healthnetworkcommunications.com

27–28 February 2017 – Amsterdam, The Netherlands
11th World Congress on Pharmaceutical Sciences and Innovations in Pharma Industry
<http://industry.pharmaceuticalconferences.com/>

27–28 February 2017 – Munich, Germany
Disposable Solutions for Biomanufacturing
www.disposablebiomanufacturing.com

27 February–2 March 2017 – Toronto, Ontario, Canada
15th Annual Cold Chain GDP and Temperature Management Logistics Summit
www.coldchainpharm.com

MARCH

6–8 March 2017 – Melbourne, Australia
8th Global Pharmacovigilance Summit
<http://globalpharmacovigilance.pharmaceuticalconferences.com/>

13–15 March 2017 – London, UK
10th International Conference and Exhibition on Pharmaceuticals & Novel Drug Delivery Systems
<http://novel-drugdelivery-systems.pharmaceuticalconferences.com/>

14–15 March 2017 – Barcelona, Spain
Parenteral Packaging
www.pda.org

16 March 2017 – London, UK
Annual General Meeting
www.jpag.org

16 March 2017 – London, UK
Assuring Data Integrity; Best Practice
www.jpag.org

19–22 March 2017 – Grenada, Spain
11th World Meeting on Pharmaceuticals, Biopharmaceutics and Pharmaceutical Technology
www.worldmeeting.org

22–24 March 2017 – Vienna, Austria
22nd Congress of the EAHP
www.eahp.eu

27–29 March 2017 – Orlando, FL, USA
International Conference on Medical Devices
<http://medicaldevices.omicsgroup.com/>

28–29 March 2017 – Dusseldorf, Germany
2017 Pharma Congress: Production and Technology
www.pharma-kongress.com

28–30 March 2017 – Bethesda, MD, USA
14th Annual Medical Device Quality Congress
<http://www.fdanews.com/mdqc>

APRIL

3–5 April 2017 – Anaheim, CA, USA
2017 PDA Annual Meeting
www.pda.org

3–6 April 2017 – Barcelona, Spain
2017 ISPE Europe Annual Conference
www.ispe.org

19–20 April 2017 – Chicago, IL, USA
World Drug Safety Congress
www.healthnetworkcommunications.com

19–21 April 2017 – Washington, DC, USA
World Orphan Drug Congress USA 2017
<http://www.terrapinn.com/conference/world-orphan-drug-congress-usa/index.stm>

20–21 April 2017 – Macclesfield, UK
APS Industrial Insights 2017
www.apsgb.co.uk

24–25 April 2017 – Frankfurt, Germany
2nd International Conference and Expo on Industrial Pharmacy
<http://industrialpharmacy.pharmaceuticalconferences.com/>

