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INVITED SPEAKER ABSTRACTS

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New approaches to solvent-free synthesis: co-crystal controlled solid-state synthesis (C^3S^3)

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The field of crystal engineering has evolved in such a manner that it has become synonymous with synthesis of new classes of organic and metal-organic compounds (Moulton and Zaworotko 2001, Zaworotko 2007). Crystal engineering invokes self-assembly of existing molecules or ions and therefore it is possible to generate a wide range of new compounds without the need to invoke covalent-bond breakage or formation. This presentation will address co-crystals, a long-known but little studied class of compounds, and their relevance to pharmaceutical science with emphasis upon their potential use in solid-state synthesis. This presentation will address the methodologies for design of co-crystals (i.e. crystal engineering) and for conversion of co-crystals to condensation products. The presentation will be organized as follows: (a) a general introduction to the when, how and why of co-crystals including their ability to modify the physical properties of active pharmaceutical ingredients (APIs; Almarsson and Zaworotko 2004, Vishweshwar et al 2006) and methodologies for preparing co-crystals such as mechanochemistry and (b) the potential impact of co-crystals on green strategies for the synthesis/processing of fine chemicals such as APIs and novel ligands will be discussed by focusing upon co-crystal-controlled solid-state synthesis (C^3S^3) (Cheney et al 2007). Particular emphasis will be placed upon condensation reactions that can afford molecular diversity with imides and imines. As revealed in Figure 1, it is possible to generate an API from starting materials using C^3S^3 (1-adamantylphthalimide). The generality of the methodology is such that hydrogen-bonding groups such as carboxylic acids do not interfere with the supramolecular chemistry needed to form the co-crystal. In many cases the product is obtained by heating the co-crystal but there are also examples of reactions which occur spontaneously under ambient conditions. C^3S^3 offers an opportunity to generate a wide range of novel compounds in a facile manner. In particular, the methodology works particularly well for molecules that contain functional groups that are capable of hydrogen bonding and it should therefore be amenable to combinatorial libraries of substrates, including those based upon renewable feedstocks.

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Vishweshwar, P. et al (2006) *J. Pharm. Sci.* **95**: 499–516
Zaworotko, M. J. (2007) *Crystal Growth Design* **7**: 4–7

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Drug delivery inspired by spiky sponges

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Silica materials are of interest in biotechnology and drug delivery (Giri et al 2007) but controllable silicate formation is very difficult. Yet a variety of sponge species make highly ordered specific glass structures called spicules (Shimizu et al 1998). Harnessing the processes that underlie this biosynthesis has considerable application. The enzyme silicatein α forms part of the organic filament found in spicules, which condenses silicate *in situ*. Both wild-type and recombinant silicatein α have been shown to catalyse the condensation of siloxanes such as tetraethoxysilane (Cha et al 1999). However, neither the wild-type nor recombinant silicatein α are amenable to biophysical study due to low levels of protein expression and inclusion body formation when recombinantly expressed in *Escherichia coli*. We recently reported silicatein α-cathepsin L chimaeras with the ability to condense silica from solution. These chimaeras are readily obtained by expression in *Pichia pastoris*, with yields around 40 mg/L of culture. The 1.5 Å crystal structure of one of these chimaeras allows us to rationalize the catalytic mechanism of silicic acid condensation (Fairhead et al 2008). This is the first report of an enzyme able to precipitate silica by condensation of the putative natural substrate, silicic acid. Characterization of the active site indicates a more likely mechanism than previously proposed by modelling of silicatein α for the condensation of alkoxysilanes. Using these chimaeras, it will now be possible to synthesize silica materials from aqueous solution at neutral pH, enabling the co-encapsulation of sensitive biological molecules. The work is immediately relevant to groups studying biomineralization processes and groups synthesizing novel silica structures for application as functional materials, such as enzyme immobilization.

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Giri, S. et al (2007) *Nanomedicine* **2**: 99–111
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Biodegradable thermo-responsive hydrogels for drug delivery and tissue engineering

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Objectives Pluronic® F127 is an A-B-A type PEO-PPO-PEO block copolymer that gels at body temperature. It has been used as a drug-delivery system and for

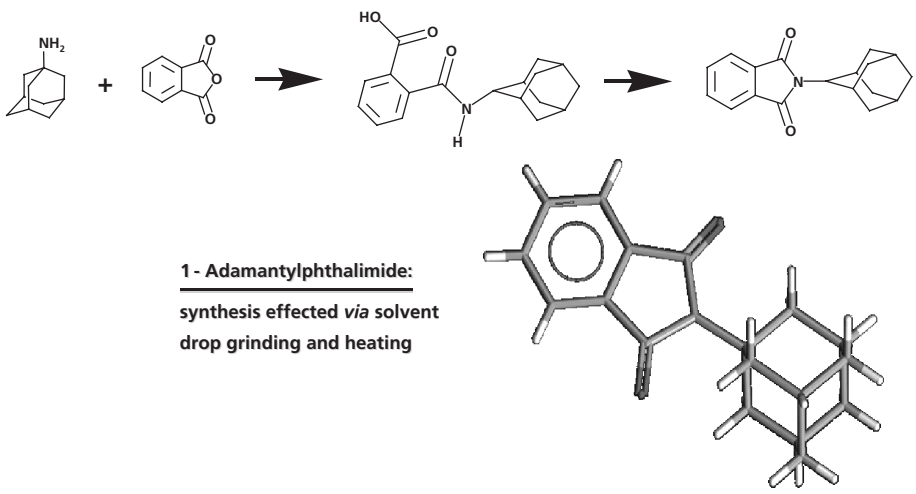

Figure 1 C^3S^3 of 1-adamantylphthalimide.

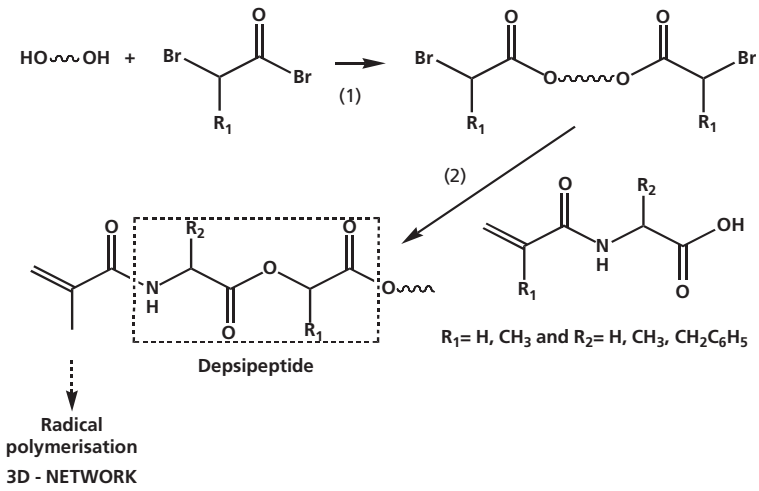

Figure 1 Schematic synthesis of crosslinkable *N*-methacryloyl-depsipeptide macromonomer.

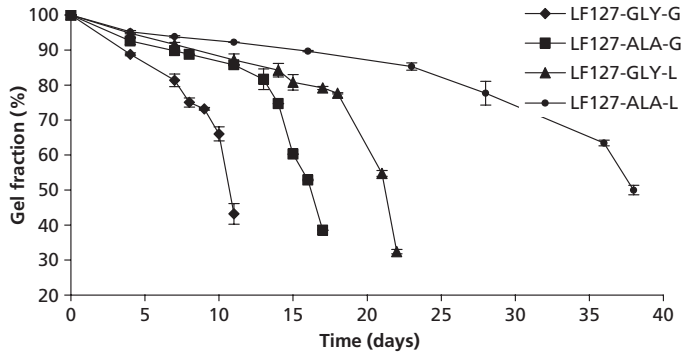

Figure 2 Influence of the hydrolytically labile end-group on the degradation rate of 30% w/w hydrogels.

implantable application (Pisel et al 2004). Unfortunately, the levels of viscosity that are attained for Pluronic® F127 gels at 37°C are not high enough for most clinical applications. They are characterized by very high permeability and short *in vivo* residence times, which make the material less suitable for most clinical applications (Sosnik et al 2003). The objective of this study was to overcome these limitations by developing biodegradable thermo-responsive systems that can be rapidly crosslinked *in vivo*, under clinically acceptable conditions.

Methods and results The Pluronic hydroxyl end groups were modified in a two-step procedure into crosslinkable *N*-methacryloyl-depsipeptide units (Figure 1). In a subsequent step, the polymers can be crosslinked to form a network structure that contains a short and well-defined hydrolytically labile sequence. In order to tailor the degradation rate, the structure of the depsipeptide unit was altered by using several α-hydroxy acids (L-lactic acid and glycolic acid) and different amino acids (glycine, alanine and phenylalanine). The influence of macromonomer concentration, photo-initiator concentration and irradiation time on the final conversion of the radical crosslinking reaction was studied by sol–gel determination, rheology and swelling tests. From these data it could be concluded that the highest conversion rate (gel fraction: ±98%) was reached in the presence of 1 mol% of photo-initiator after an UV irradiation of 30 minutes. The thermo-responsive properties were preserved after crosslinking. The *in vitro* degradation, performed in phosphate-buffered saline at 37°C, demonstrated that the degradation rate can be tailored by changing the R side groups of the depsipeptide units. Steric hindrance and hydrophobic effects influence the hydrolysis of the labile ester bonds resulting in an increased degradation rate ranging from 10 to 40 days (Figure 2). Drug-release patterns of high-molecular-mass drugs were investigated using bovine serum albumin (BSA; 68 kDa) and FITC-dextran (260 kDa) as models. It was demonstrated that the macromolecules are entrapped in the polymer network and released by polymer swelling and degradation. The biodegradable gels have also been used for the immobilization of bone marrow cells cultured on microcarriers. Different microcarriers, including porous crosslinked gelatins, alginates and calcium phosphates, were studied. Fluorescence microscopy and immunostaining proved that the cells could be cultured on the carriers and then immobilized in the biodegradable thermoresponsive hydrogel. Good cell viability was observed for at least 3 weeks. The first data from cell differentiation studies give encouraging results. These will be discussed at the meeting.

Conclusions Starting from Pluronic F127 photo-crosslinkable biodegradable hydrogels can be prepared. The rate of degradation can be fine-tuned by the structure of the biodegradable segments. Drug-release studies showed sustained release patterns for macromolecular drugs. The gels also show promise as a matrix for cell immobilization and hence as scaffolds for tissue engineering.

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Sosnik, A. et al (2003) *J. Biomat. Sci Polymer Edition* **14**: 227–239

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Warfarin pharmacogenetics: ready for clinical implementation?

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Objectives Warfarin is the most commonly used anti-coagulant in the UK; its efficacy depends on maintaining anti-coagulation within a therapeutic range but this is difficult because of its narrow therapeutic index. Previous retrospective studies, including patients already on maintenance dose, have built dosing algorithms, representing environmental factors and the genes *CYP2C9* and *VKORC1*, to explain over 50% of variability in dose requirements. Their effectiveness in prospectively estimating maintenance dose in patients being initiated on to warfarin, however, is unclear. To accurately evaluate the true impact of environmental and genetic factors on treatment response in such patients, a prospective study was undertaken. In addition to genes *CYP2C9* and *VKORC1*, variants in a further 27 candidate genes were genotyped.

Methods 1000 patients being initiated on to warfarin were recruited. Patient demographics were recorded and a blood sample taken for DNA. Study visits were conducted at 1, 8 and 26 weeks. All international normalized ratio (INR)

measurements, warfarin dose changes and adverse events during follow-up were recorded. In addition to bleeding events the following outcomes were assessed: INR > 4 during the first week; warfarin sensitivity; warfarin resistance; time to maintenance dose; time to therapeutic INR; maintenance dose. Univariate analyses assessed association between each single nucleotide polymorphism (SNP) and outcome. Multiple regression models investigated the association with each individual gene. Statistical significance was assessed using the false discovery rate (FDR).

Results and conclusions In an interim analysis including 311 patients only one SNP, in clotting factor V gene, was associated with bleeding risk. In the multiple regressions no gene was significant. Power was limited, however, by the small number of bleeding events (n = 16). For the remaining outcomes, *CYP2C9* and *VKORC1* were the most significant, with *CYP2C9* more important during the initiation phase and *VKORC1* more important in the maintenance phase. Since maintenance dose can be closely regulated by INR monitoring, future dosing algorithms should focus on outcomes relevant during the initiation phase, where *CYP2C9* is the prominent gene.

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Green analytical chemistry in Pfizer

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Although the principles of green chemistry are becoming firmly established as a mechanism to synthesize pharmaceutically active compounds, the area of green analytical chemistry is an immature field in the pharmaceutical industry. Within Pfizer, an Analytical Green Chemistry team was established to identify and promote potential green analytical chemistry practices for pharmaceutical analysis. This presentation will highlight some initial thoughts on green analytical chemistry, including (a) analytical technique selection (e.g. what techniques could be considered 'green'), (b) sample preparation (e.g. comparison of solvent used for sample preparation versus analysis), (c) analytical instrument power usage (e.g. conventional versus ultra-high-performance liquid chromatography), (d) infrastructure costs (i.e. solvent usage and electrical power consumption), (e) solvent and buffer choice considerations, (f) super-heated water and super-critical CO_2 as solvents and (g) process analytical technology, and accompanied by relevant examples from the literature and generated internally in Pfizer.

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Safety and efficacy of microneedles for painless intra-epidermal delivery of DNA and vaccines

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Amid recent calls for expansion of the routine vaccination schedule in the UK (e.g. hepatitis B, human papilloma virus) and, paradoxically, heightened sensitivity of the public towards the safety of vaccines, developments in vaccination technology are extremely timely. In a climate of worldwide concern over an influenza pandemic, more efficient and safer methods for distributing and delivering vaccine are particularly relevant. Traditional intra-muscular vaccination is painful and relies on administration by a healthcare professional. Intra-dermal immunization provides an alternative route for vaccine delivery, potentially offering a dose-sparing effect whereby reduced volumes of antigen can produce protective immune responses through targeting immune-responsive cell populations resident in skin. Microneedle arrays consist of a plurality of individual microprojections that are engineered to an appropriate length (e.g. 200–400 μm) to penetrate the outer barrier layer of skin, providing transient pathways for accessing epidermal Langerhans cells and dermal dendritic cells, without impacting on underlying pain receptors or blood vessels. Microneedle-based vaccines could offer significant benefits in Western and developing-world immunization schemes (mass-transportable, self-administrable and safe disposal), in children/needlephobes (improved compliance with reduced distress) and in response to pandemic outbreaks (rapid mass vaccination, dose-sparing).

We have demonstrated the potential of prototype microneedles for the safe and efficient cutaneous delivery of both vaccines and DNA vaccines, which produce antigen *in situ* and are potentially more proficient, stable and suited to rapid mass production. Our microneedle group combines pharmaceutical, dermatological, pharmacy practice and engineering specialists from the Welsh School of Pharmacy, Cardiff School of Medicine and Cardiff School of Engineering with external engineering and clinical expertise at Tyndall National Institute, Ireland, and Gwent Healthcare NHS Trust. Microneedle designs of variant morphology and material composition have been fabricated and characterized by light and scanning electron microscopy. Preliminary investigations are undertaken in *ex vivo* human skin, obtained from surgery with ethical approval and informed consent and maintained in a validated organ culture system. Staining of skin puncture marks with external dye and trans-epidermal water loss measurements have shown successful penetration of the stratum corneum with an approximately 2–3-fold increase in water flux across the skin surface. Microneedle-facilitated delivery of hepatitis B surface antigen (HBsAg) has shown efficient epidermal localization through transverse sectioning and immunohistochemistry. Positive expression of HBsAg from pCMVHB-S2.S, a DNA vaccine encoding HBsAg, was confined to the epidermis and clearly associated with microneedle-created channels of approximately 150 μm depth. In a clinical study of 12 subjects receiving single-blinded insertions of a 25-gauge hypodermic needle and two microneedle arrays (of either 180 or 280 μm needle height) microneedle application caused significantly less pain and discomforting sensation than the hypodermic needle. Skin damage was minimal with evidence of microchannel repair and resealing apparent at 8–24 hours post-application. Microneedles offer a pain-free, self-administrable, mass-distributable, readily disposable and potentially more efficient method for vaccination and warrant further clinical investigation. Our laboratory is currently collaborating with Georgia Institute of Technology and Emory University to explore the future role of microneedles in pandemic influenza.

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Tamoxifen pharmacogenetics: implications for breast cancer treatment

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Tamoxifen is a standard endocrine therapy for the prevention and treatment of steroid hormone receptor-positive breast cancer. Tamoxifen requires enzymatic activation by CYP450 enzymes for the formation of the clinically relevant metabolites 4-OH-tamoxifen and endoxifen, which both have a greater affinity for the oestrogen receptor and the ability to inhibit cell proliferation when compared with the parent drug. CYP2D6 is the key enzyme in this biotransformation and recent mechanistic, pharmacological and clinical pharmacogenetic evidence suggests that genetic variants and drug interaction by CYP2D6 inhibitors influence plasma concentrations of active tamoxifen metabolites and outcome of patients treated with adjuvant tamoxifen. Particularly, non-functional (poor metabolizer, PM) and severely impaired (intermediate metabolizer, IM) CYP2D6 variants are associated with higher recurrence rates. Their frequency in individuals of European descent ranges between 10 and 20%, leaving these individuals with little or no capacity to convert tamoxifen into clinically relevant metabolites. Several studies in post-menopausal patients with oestrogen receptor-positive breast cancer, including our own, showed that patients with PM and IM genotypes had shorter relapse-free time (hazard ratio 2.24, 95% confidence interval 1.16–4.33) and event-free survival (hazard ratio 1.89, 95% confidence interval 1.10–3.25) when compared with patients with two functional CYP2D6 alleles (Schroth et al 2007). If these findings can be replicated in large studies, then CYP2D6 genotyping prior to treatment for the prediction of metabolizer status and outcome may open new avenues for the individualization of endocrine treatment choice and benefit.

Schroth, W. et al (2007) *J. Clin. Oncol.* **25**: 5187–5193

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Antibiotic treatment of chronic infections: time for a new paradigm?

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Whereas concern over anti-microbial resistance has dominated public debate, the lack of efficacy in the use of existing anti-microbials against chronic infections remains a pressing issue in patient treatment. Poor outcomes of treatment can generally be attributed to the reduced susceptibility of biofilms, which are associated with chronic, recurrent and device-related infections and may account for more than 70% of human infections. This reduced susceptibility of biofilms is complex and considered by many to be multifactorial. We have used the Calgary Biofilm Device, a lid having 96 pegs that sit in a standard 96-well plate, to provide the first simple mechanism to form multiple equivalent biofilms under shear force, to address the mechanisms of reduced biofilm susceptibility to antibiotics and other anti-microbials. Our data support the belief that biofilm tolerance to anti-microbials is a result of phenotypic diversity of the population, initiated by adhesion or aggregation early in biofilm formation, resulting in the multifactorial change to susceptibility. We have shown that structural organization of the

community, including the complex extracellular matrix surrounding the biofilm, results in a spatial organization of the biofilm-forming gradients of oxygen and nutrients that contributes to the biofilm's anti-microbial tolerant phenotype. Further communication between cells making up the population serves to enhance greater phenotypic diversity, and an increase in persister cells within the biofilm population, leading to greater anti-microbial resistance. Our studies employing the Calgary Biofilm Device have also pointed to the enhanced efficacy of biofilm treatment by combinatorial antibiotic therapy, suggesting a shift in the paradigm away from the minimal inhibitory test as a means for selecting anti-microbial therapy and providing a selection mechanism for next-generation antibiotics with efficacy against biofilms.

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Drug-eluting beads: a new paradigm in the treatment of liver cancer

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Transarterial chemoembolization (TACE) has been used for many years in the treatment of hypervascularized tumours. The dual blood supply to the liver allows for the embolization of selected arteries, which are predominantly responsible for providing nutrients and oxygen to the tumours. Although it has been demonstrated in randomized studies that there is a survival benefit (Llovet et al 2002) of chemoembolization versus best supportive care, the TACE procedure varies vastly in clinical practice, leading to inconsistent outcomes. Drug-eluting beads (DEBs) are sulphonate-modified polyvinyl alcohol hydrogel microspheres and have been developed to affect intra-arterial delivery of chemotherapeutic agents over a sustained period in a controlled manner, deliver a high concentration of drug local to the site of the tumour, reduce the systemic exposure to free drug and occlude the tumour arterial blood supply. DEB Doxorubicin and Irinotecan have been shown to be actively sequestered and released by the DEBs via an ion-exchange phenomenon (Gonzalez et al 2007). DEBs have been well characterized *in vitro* with respect to drug loading and elution kinetics and effects on the physical attributes of the beads related to catheter delivery (Lewis et al 2006). These drug-device combinations have been evaluated in a number of pre-clinical models that demonstrate the concept of high local delivery of the drug combined with lower systemic exposure. These data are supported by encouraging preliminary phase I/II clinical results in the treatment of both hepatocellular carcinoma and metastatic colorectal cancer of the liver. Varela et al (2007) have demonstrated significant reductions and less variation in the C_{max} and area under the curve of plasma doxorubicin for DEB-TACE compared with conventional TACE, with a tumour response rate of 75% by European Association for the Study of the Liver (EASL) criteria (Varela et al 2007) compared with historical control rate of 35% (Llovet et al 2002). The 1 and 2 year survival rates for the DEB-TACE group were 92.5 and 88.9% respectively compared with historical values of 82 and 63% (Llovet et al 2002). This presentation will provide an overview of the bench-to-bedside development of these drug-device combinations for the treatment of liver cancer.

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Lewis, A. L. et al (2006) *J. Vasc. Interv. Radiol.* **17**(2 Pt 1): 335–342
Llovet, J. M. et al (2002) *Lancet* **359**: 1734–1739
Varela, M. et al (2007) *J. Hepatol.* **46**: 474–481

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Excipients: characterization of mechanical properties

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In the selection of materials for tablet formulation, it may be possible to evaluate and optimize the robustness of a formulation to conditions of manufacture by empirical testing in a production environment. However, the supply and cost of raw materials limits the viability of a production-scale approach to formulation design. It is generally more desirable and cost-effective to evaluate production behaviour at a laboratory or pilot scale using a combination of material property measurements and small-scale simulations of the manufacturing process. The experimental methods of bulk powder characterization are briefly described together with the practical application of compaction simulation to formulation design and process scale-up. The processing properties of excipients for tablet formulation can be assessed using measurements of mechanical properties such as compressibility and tensile strength. It is then possible to assemble a database of excipient properties to support decisions in the development of a new product. Whereas a database of excipient material properties is a valuable aid to excipient selection for tabletting, a number of challenges remain in the practice of developing solid dosage formulations. In particular, excipient selection for formulation design could be facilitated by (a) prediction of the properties of mixtures from the properties of the individual components, (b) understanding the effects of the intermediate processing steps of mixing and granulation and (c) correlating bulk powder properties with particle scale characteristics. The evolution of methods for formulation development using 'scaleable' material parameters and the potential of computational methods for future developments in predictive tablet processing are discussed.

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Estimation of intra-luminal dissolution rates: media for simulating conditions in stomach and in the small intestine

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Intra-luminal drug concentrations influence the rate of appearance in plasma and, under certain circumstances, they can govern the total amount of drug reaching the general circulation. They can be measured directly or by using imaging techniques but both approaches are associated with ethical issues and/or high costs. One way to eliminate these drawbacks would be collect human aspirates without prior administration of the drug and use them for measuring the parameter of interest. Determining solubility in human aspirates should be able to help estimate intra-luminal dissolution kinetics much better than studying solubility in simple aqueous solutions. Further, since the use of human aspirates in *in vitro* dissolution testing is limited by volume availability, solubility data in human aspirates could also be used to confirm the biorelevance of media designed to simulate the intra-luminal conditions. Provided that hydrodynamics are appropriately taken into consideration, biorelevant media can then be used in *in vitro* dissolution experiments for estimating the intra-luminal drug concentrations. In this presentation, the importance of using biorelevant media for estimating intra-luminal solubility and dissolution rates will be shown with specific examples. In addition, based on data collected recently in humans, an update of the composition of biorelevant media to represent the composition and physical chemical characteristics of the upper gastrointestinal fluids as closely as possible while providing physical stability during dissolution runs and short-term storage will be presented. Specifically, four intra-luminal conditions will be considered; the stomach in the fasted and fed states and the small intestine under the corresponding conditions. For the fed state, simulating media approaches to take into account the changing intra-luminal environment in that state will also be discussed. Updated biorelevant media have been proved to be stable under ambient storage conditions for at least 72 hours as well as under usual dissolution test conditions.

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Engineered composites for endodontic surgery

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Endodontics deals with the treatment of the tooth pulp and surrounding root of the tooth. On presentation for endodontic treatment, the dentist will usually be dealing with infections of the root and perhaps also abscess formation, all of which have significant bacterial contamination. One of the major material requirements is a root sealer and the primary role of this is to prevent further infection via the interface between the tooth and the sealer. Currently used materials tend to act as a plug to prevent further bacterial ingress and one of the major materials used is Gutta Percha, but these materials are in general inert or passive. However, current therapies have significant levels of reinfection associated with them and thus we have worked to develop a more effective sealer. Recent work has investigated the use of phosphate-based glasses in both PHB-based polymers and also more recently in polycaprolactone, which has been shown to provide a highly effective marginal seal with the rapid formation of calcium phosphate at the margins. We are also working towards a material with anti-bacterial properties and this will be described here. In the long term we aim to investigate whether the release of calcium and phosphate ions may drive the longer-term remineralization process.

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Quality formulation design: application of the principle of Quality by Design to formulation design

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The Quality by Design (QbD) approach to pharmaceutical development and regulatory submission has primarily focused on identifying the critical quality attributes (CQAs) of the formulation followed by the identification of the critical formulation and process variables that independently or synergistically affect the CQAs. Design of experiment (DOE) is then used to define a design and control space for the critical formulation and process variables. The QbD approach to development has been accepted and adopted by industry over the last 5 years and the focus has been on the late-stage development projects where the formulation and process have been fixed during phase II and early phase III development stages. This has resulted in building a QbD rationale into already-defined formulations and processes. This approach has been shown to be effective in demonstrating understanding and defining a control strategy for the formulation and manufacturing process. The effort and resources involved in reverse engineering the formulation and manufacturing process to gain the necessary scientific understanding to demonstrate that QbD has been applied can seem disproportionate to the benefit gained. With the maturation of QbD development processes within the industry and the opportunity to apply these processes in early-stage development the ability to design quality into the formulation and process before scale-up to commercial operations now exists. This has the potential benefit of reducing the effort and resources that are currently applied to achieve a QbD regulatory submission. QbD is not a new concept: in its simplest form it can be described as good scientific practice. Pharmaceutical formulation scientists have applied good scientific practice to formulation development for decades with much success. The approach to formulation development in this current QbD development climate requires a shift in focus for the formulator. The formulator now needs to consider what the CQAs will be and what formulation and process variables could affect the CQAs. The formulator will now conduct small-scale DOEs to understand the critical variables' effects on the CQAs and develop the necessary scientific rationales to focus the large-scale DOE experimentation and develop the control strategy. The aim is now to produce formulations and processes which are robust and suitable for scale-up and a QbD submission. The formulation scientist has a myriad of analytical and science of scale tools that can be applied in formulation development that will aid the production of a QbD formulation and manufacturing process. Over the next few years the benefit of applying these tools in early formulation development will become apparent as reverse engineering of formulations and processes will no longer be the first stage of QbD development and full-scale DOE experiments will be focused and reduced in number and scale.

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Triggered drug delivery from biomaterials: mobilizing the charge and light brigades

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Irrespective of their position of implantation, a ubiquitous problem associated with implanted biomaterials and medical devices is infection. For example, ventilator-associated pneumonia, which arises in patients who are mechanically ventilated via an endotracheal tube for at least 48 hours, has an incidence which can be as high as 67% despite the use of complex antibiotic regimens; continuous ambulatory peritoneal dialysis (CAPD) patients suffer rates of infection approaching 100%. It is therefore generally accepted that there exists an urgent need to develop novel strategies to reduce the incidence of infection in implanted biomaterials and medical devices. While passive diffusion strategies have had significant success in some applications, the ability to control the release of therapeutics from a polymeric delivery platform remains a key goal in the development of advanced medical polymers which are resistant to bacterial colonization. Our research focuses on developing polymers capable of releasing a drug according to 'smart' mechanisms or following the application of an appropriate trigger. Our systems can frequently be tailored to give the release profile required – this may be where a strong 'burst' release of drug is required, such as at the onset of medical device infection – or to situations where sustained zero-order delivery of therapeutic agents is required, particularly at difficult-to-address sites such as joint replacements, and is difficult to achieve by conventional drug-incorporation strategies. The trigger to drug release may be applied externally, or be triggered internally by a specific marker, such as chemical species generated at the onset of infection. Such systems are a move towards ideal drug-delivery systems, where a precise amount of drug is released to a precise location when required. This paper describes the applicability of triggers such as light, heat, magnetism, ultrasound and chemical triggers such as pH. In particular, the use of light to precisely control drug doses (potentially with molecule-scale control) from optically responsive hydrogels, and chemically responsive materials based on charged copolymers, will be highlighted and their potential applications explored.

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Facile production of composite nanoparticles for drug delivery, targeting and imaging

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Nanoparticle formulations of hydrophobic drugs present unique opportunities for treatment of solid tumour cancers, for delivery of drugs by aerosol administration and as a route to novel vaccine adjuvants. The common requirements of these applications are precise control of particle size and surface functionality. For cancer therapy, particles in the size range of 100–200 nm passively pass through defects in the vasculature in tumours and deposit by 'enhanced permeation retention'. In addition to delivery, the ability to monitor the fate of the nanoparticles is also important since anti-cancer agents are invariably toxic to healthy tissue. Our process – Flash NanoPrecipitation – a controlled precipitation process that produces stable nanoparticles at high concentrations using amphiphilic diblock copolymers to direct self-assembly, enables the production of composite nanoparticles that enable simultaneous imaging and delivery. Uniform particles with tunable sizes from 50–500 nm can be prepared in an economical and scalable manner. The key to the process is the control of time scales for micromixing, polymer self-assembly, and particle nucleation and growth. The poly(ethylene glycol) (PEG) protective layer creates long-circulating particles and the inclusion of PEG chains with terminal ligands allows drug targeting. The incorporation of gold nanoparticles, magnetic nanoparticles or fluorophores into the composite particle enables imaging by X-ray, magnetic resonance imaging or confocal microscopy, respectively. The incorporation of up-converting phosphor crystals into the composite nanoparticles enables a highly efficient form of photodynamic therapy.

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Pharmacogenetics of cancer: current progress, challenges and opportunities

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The Human Genome Project has led to the discovery of DNA sequence variants, the majority of them being single nucleotide polymorphisms (SNPs) and gene amplifications. The potential influence of DNA variation on the activity and/or adverse reaction of cancer chemotherapy is being investigated. Pharmacogenetics and pharmacogenomics are gaining momentum and their application to current cancer treatment and drug discovery is of high priority. The number of studies reporting a relationship between DNA sequence variants and cancer treatment outcome are increasing in number. In particular, the following associations were found: *DPYD* gene mutations and severe 5-fluorouracil (5-FU) toxicity (Ezzeldin et al 2003), *EGFR* mutations and responsiveness of non-small cell lung cancer (NSCLC) to gefitinib (Lynch et al 2004), *ERCC1* polymorphisms and severe drug toxicity in NSCLC patients (Suk et al 2005), genetic variants in the *UGT1A1* gene and severe neutropenia by irinotecan (Innocenti et al 2004), *MTHFR* genotype and treatment response in pediatric acute lymphoblastic leukemia (ALL) (Aplenc et al 2005), *TS* and *MTHFR* gene polymorphisms in normal tissue and 5-FU sensitivity (Jakobsen et al 2005), *TPMT* genotype and early treatment response to 6-mercaptopurine in childhood ALL (Stanulla et al 2005) and *CDA* genotype and response to gemcitabine in NSCLC (Tibaldi et al 2008). The next step in pharmacogenetic research should be the validation of these findings in randomized prospective trials, specifically designed to compare the outcome of treatment selected on the basis of patient's genotype (normal tissue compared with tumour) compared with standard approach. In conclusion, the improvement in genotyping technologies and the availability of high-density SNP maps, combined with efficient and cost-effective analytical methods, open the possibility of fulfilling the promise of reducing the toxicity burden and personalizing the treatment offered to cancer patients.

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Herbal medical products: how can we establish therapeutic equivalence?

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From a consumer's perspective, it is normally not transparent what the differences are between two products which contain 'identical herbs'. Herbal medical products (HMPs) also offer unique and complex challenges to the analyst. Clearly, they are a mixture of active and inactive substances, with other substances making an indirect contribution to the effect. One of the main strategies for developing high-quality products, advocated over recent years, is standardization. This is achieved by defining minimum (and sometimes maximum) amounts of one or several compounds or groups of compounds in a phytopharmaceutical product, which could also form the basis for developing therapeutic equivalence. Cinnamon has become a popular over-the-counter preparation for the management of diabetes. *Cinnamon ceylanicum* NEES and *Cinnamomum cassia* BLUME are both used but show significant differences in their anti-oxidant and phytochemical profile, but on the other hand show similar effects on the glucose metabolism (Feistel 2007). High-performance liquid chromatography analysis has proven to be an ideal method for a comparative assessment. *Echinacea* is commonly used for treating symptoms associated with colds and other respiratory conditions and is also used as a preventive HMP. We recently investigated the interaction potential of *Echinacea* liquid preparations and found that the products showed an enormous variability in terms of the IC50 values for CYP3A4. In assessing other studies we found that generally insufficient experimental information is available for several of the studies, limiting their usefulness. Consequently, it is also not possible to systematically compare the studies with respect to these conditions and their impact on the outcomes. This example highlights the need to ascertain that a full pharmaceutical analysis is included in studies on an HMP's pharmacological effects or clinical effectiveness and shows that standardization is not yet possible since the active constituents are only known partially. *Cannabis sativa* L. is currently at the centre of numerous clinical and pharmacological studies. We recently used a metabolomic fingerprinting of extracts to understand the differences in composition and *in vitro* pharmacological effects of hot- and cold-water extracts as well as ethanol/water mixtures (tinctures) of cannabis. This approach may offer a novel and unique strategy to establish therapeutic equivalence of plant tinctures.

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Patchy responses to transdermal delivery

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Transdermal delivery aims to deliver systemically active levels of the therapeutic ingredient, as opposed to topical delivery where local or regional effects are desired. However, transdermal delivery inevitably produces some degree of local accumulation of the drug at the site of application, which could potentially sensitize or irritate the viable tissue in contact with the delivery device. Evaluating comparability of transdermal systems is problematic and it is important to define the purpose of the comparison. For example, comparability could be shown through *in vitro* release testing, essentially employing an artificial inert membrane and determining kinetics from the amounts of drug released through the membrane with time, or the US Pharmacopoeia (USP) 'paddle over disc' (Apparatus 5) method. This approach is a valuable quality-assessment tool for assuring batch-to-batch uniformity, detecting manufacturing changes that influence drug-release properties or for developing and optimizing formulations. However, without a skin membrane, such studies reveal little information as to potential systemic drug loads from a transdermal device. *In vitro* permeation studies using human skin membranes do offer some insight into potential systemic delivery levels. By applying the delivery device to a skin membrane housed in a Franz-type diffusion cell, amounts traversing the tissue with time can be determined, as can residual amounts remaining in both the skin and the delivery device. Further, formulation can be optimized using this method, which can also serve as a quality-assessment tool. Again there are significant limitations with this approach, for example using non-viable (metabolically compromised) tissue which is removed from the systemic circulation or the use of non-physiological receptor solutions to receive the drug traversing the tissue. Transdermal delivery systems are typically regarded as controlled-release dosage forms and regulatory bodies consider them as new drug applications (or abbreviated new drug applications). Consequently, bioavailability and/or bioequivalence studies are required and typically use a similar approach to that for oral drug delivery: plasma concentration-time profiles (area under the curve) can be used to evaluate bioavailability and so two products with similar profiles can be considered to be bioequivalent. Such studies are now standardized with bioequivalence at 80–125% required with a confidence interval of 90% for test product approval. Again there are some caveats in that different transdermal devices could contain different amounts of the same drug, but deliver them equally (i.e. provide the same plasma concentration/time profile) and so be considered bioequivalent, but would be pharmaceutically inequivalent. Equally, two transdermal delivery systems containing the same amount of active ingredient could deliver them to different degrees. Comparability of transdermal patches also extends to patient compliance and in-use performance. Patch sizes may differ but could deliver similar plasma drug levels. Patch adhesivity could vary, affecting, for example, ease of removal. So, tack- and wear-testing is also important in comparisons of transdermal drug-delivery systems.

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Comparability of vaccine products: same disease, different vaccines

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The concept of bio-similars applies as much to vaccines as to other biopharmaceuticals and has been a factor since the earliest history of vaccination although the implications were recognized much more recently. Thus, smallpox vaccine encompassed a wide range of vaccinia strains (and possibly viruses that were not vaccinia) with widely varying reactogenicity patterns. Similarly, Bacille Calmette–Guérin (BCG) vaccines cover a wide range of sub-strains with differing genetic composition and biological properties. Although this is suspected to affect vaccine performance, clinical evidence is sparse as numerous variables exist and few sub-strains have been compared in side-by-side studies. Similar situations occur with many other vaccines, including measles, mumps and rubella vaccines, where evidence of variations in reactogenicity and immunogenicity has been related to the use of different attenuated virus strains. Hepatitis B vaccines produced by recombinant technology have shown differences in seroconversion rate depending on cell substrate and production process used. In the case of pertussis vaccines, wide variations in reactogenicity and efficacy have been reported for different whole-cell vaccines. This may relate to difficulties in achieving product consistency as much as to variations in product design. For acellular pertussis vaccines variations in composition, method of detoxification and formulation have been reflected in differences in efficacy in clinical trials although the reactogenicity profiles have been consistently low. In the case of conjugate vaccines against *Haemophilus influenzae* b and *Neisseria meningitidis* serogroup C preparations differing in carrier protein, saccharide chain length and conjugation technology have been developed. Whereas these may show differences in immunogenicity in clinical studies, all have proved efficacious in use. Bio-similarity is a significant issue for vaccines and can only be addressed by careful clinical evaluation at pre-licensing stage.

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Developing dementia research capacity in the community: lessons from the DENDRON network

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UK government policy is to maintain people with dementia syndromes in their own homes for as long as possible. However, the needs of people with dementia and their carers are inadequately addressed, from diagnosis through to end-of-life care. There are multiple obstacles to the timely recognition of dementia syndromes in primary care, and support for people with dementia and their families after diagnosis is limited. Carer strain is not reduced often enough by timely, skilled and sensitive interventions. The therapeutic options available to clinicians are sparse and insufficiently evaluated. On the other hand, there are effective symptom-modifying treatments for people with Alzheimer's disease and more pharmacological treatments are in the pipeline. The next target for chemotherapeutic

approaches in dementia is the development of disease-modifying drugs, but this concept is controversial and the design of these trials raises many questions. Which populations should be studied? For how long? With which principal and secondary end points? Are surrogate markers available? There is a lot to be gained from the study of patients who reflect the population at risk because measures of absolute effectiveness, absolute harm and cost-effectiveness are associated with underlying risk levels in different socio-demographic groups and under-representation will therefore bias absolute effect estimates. Primary care-led studies could in theory address these methodological problems, but in practice we know from recent trials that recruitment to studies on dementia through general practice is problematic. Dementia research in England and Wales is now supported by DENDRON (Dementia & Neurodegenerative Diseases Research Networks), which is attempting to address these methodological problems. DENDRON has promoted the development of research capacity for dementia studies in primary care by two methods: investing in practice recruitment across the network and organizing primary care researchers from different disciplines into a Clinical Study Group that will develop a research agenda and work up studies for the research network. This presentation will (1) describe the methods used to identify 200 practices with an interest in hosting dementia research and (2) report on the studies developed by Clinical Study Group members that are underway or at an advanced stage.

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Ocular drug delivery: the role of drug/device combinations

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The presence of the blood–retinal barrier causes ocular-specific complications for the delivery of therapeutic levels of drugs to the eye. There is a challenge to design and evaluate potential drug-delivery routes by incorporation of drugs into the ocular implants and the control of their release kinetics. Ocular implants include devices such as contact lenses, intraocular lenses (IOLs) and tamponade agents. Incorporation of drugs into these devices could provide routes to treat diseases such as glaucoma, proliferative vitreoretinopathy (PVR), endophthalmitis and posterior capsule opacification (PCO). The majority of ophthalmic drugs are delivered to the eye topically via drops; however, it is well known that this is highly inefficient, resulting in only around 5% penetrating the cornea and reaching the ocular tissues. The remaining drug is either lost via the lacrimal duct or absorbed by the conjunctival tissues. One route to overcome this wastage and increase the amount of drug reaching the relevant areas within the eye is to incorporate the active ingredients within a contact lens. The contact lens sits on a thin tear film and has the potential to release the drug from the lens material and trap it against the cornea. It has been shown that this significantly increases the availability of the drugs to the ocular tissues. The delivery of a range of drugs via this method has been reported, including β-blockers to treat glaucoma, steroids to treat inflammation and antibiotics to treat infection.

A significant clinical problem that occurs following cataract surgery and the implantation of an IOL is PCO. PCO results from the migration of lens epithelial cells on to the posterior capsule. Trans-differentiation of these cells into fibroblast-like cells and the fibrosis and contraction can cause a healing response that influences optical clarity. A potential route to modulate this response is the incorporation of anti-proliferative apoptosis-inducing or cell-adhesion-blocking agents with the IOL at the time of surgery. To reduce the toxicity of these agents various ways of attaching the drugs to the IOL surface or dispersion of the drug within the IOL, so that its rate of release is controlled, are under investigation. PVR is characterized by cell migration, proliferation and contraction in the vitreous cavity following retinal detachment. The surgical treatment of retinal detachment often involves the replacement of the vitreous with a tamponade agent. The role of the tamponade agent is to close the retinal tear and the most common long-term tamponade agent is silicone oil. Although this has improved the clinical success significantly, re-detachment due to PVR is still a clinical challenge. The application of anti-inflammatory and anti-proliferative drugs to control PVR has some potential but there remains a need to determine a procedure to deliver therapeutic doses over extended time periods into the vitreous cavity. The development of tamponade agents with the potential to act as drug-delivery systems is under investigation.

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pH-responsive diethylstilbestrol-polyacetals for the treatment of hormone-dependent cancers

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The development of better polymeric carriers is an ongoing challenge. There is a need to develop high-molecular-mass, biodegradable polymeric carriers that can better exploit enhanced permeability and retention (EPR)-mediated tumour targeting (Greco and Vicent 2008). Additionally, there is an urgent need to move away from heterogeneous, random-coiled, polymeric carriers towards better-defined polymer structures. Within this context, we have previously designed pH-responsive polymers into which a drug can be incorporated within the polymer backbone, allowing controlled release on exposure to a decrease in pH (tumour interstitium, intracellular endosomal/lysosomal compartments). We used synthetic non-steroidal oestrogen diethylstilbestrol (DES) as model drug. These linear DES-polyacetals are the first water-soluble anti-cancer polymeric drugs designed for acidic pH-triggered release of a drug incorporated into the polymer main chain (Vicent et al 2004). To obtain a second-generation construct with improved characteristics, such as lower polydispersity or higher drug capacity, novel amphiphilic block copolymer analogues, DES-*co*-polyacetal-*b*-PEG-*co*-polyacetals (PEG is poly(ethylene glycol)), were developed. These systems showed a demonstrated lower polydispersity and a higher drug capacity. As expected, the block copolymer synthesized underwent pH-dependent degradation with a much faster rate of DES release at acidic pH, in order to mainly liberate the bioactive trans-DES form. The block copolymer also displayed greater cytotoxicity against human prostate and breast cancer cell lines when compared with the random terpolymer. This fact could be explained by the different conformations adopted by the conjugates in solution. A different conformation could influence drug-release kinetics and, therefore, their therapeutic outcome. Polymeric micelle formation could be also achieved under the appropriate conditions. To demonstrate the therapeutic value of these polyacetalic systems, *in vivo* studies using xenograft mouse models are being currently carried out with very promising results.

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Bone morphogenetic proteins as therapeutic agents for tissue regeneration

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The past decade has witnessed some exciting developments in tissue engineering, including the innovative use of a host of protein and bioactive growth factors which have reported beneficial and therapeutic effects on a variety of tissues *in vitro* as well as *in vivo*. One such group of growth factors – bone morphogenetic proteins (BMPs) – has been the focus of attention particularly for the treatment of bone defects where slow healing rates and poor quality of regenerated tissue are important concerns. In order to understand the role of BMPs as drug agents and to evaluate their therapeutic potential, suitable delivery systems have been developed and yet these have shown limited success *in vivo*. Some of the more commonly utilized devices will be highlighted in this presentation. Whereas some of the therapies and techniques currently under investigation offer some insights to the mode of tissue regeneration, there remain several important questions concerning the mechanism of action of the BMPs. Thus, the important role of BMP receptors and how these may mediate BMP-induced bone cell function will be discussed. Finally, current trends and future therapies involving BMPs will be presented with emphasis on prospective gene-related therapies. The recent advances in the biochemistry of BMPs and their receptors augur well for new and realistic strategies to engineer the regeneration of bone and related tissues.

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Animal models of cognition and putative novel therapies

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Learning and memory are commonly assessed in animals using methods such as passive or conditioned avoidance and mazes. Passive and conditioned avoidance tasks are measures of associative learning coupled with reward or punishment, whereas mazes assess spatial memory. The relevance of these tests as models of the human clinical conditions where there are multiple facets of the disorder is questionable. The novel object recognition task (Ennaceur and Delacour 1988) was developed as a task to measure working memory, attention, anxiety and preference for novelty in rodents. This task is particularly attractive as a model for human cognitive impairment as it requires no external motivation or reward, no punishment and little training or habituation. Interestingly, since its development it has become apparent that there are strain differences in rat and mouse performance in the test, with, for example, the DBA/2 strain of mouse being particularly poor at novel object recognition (Gard and Pavli 2004). This observation is particularly pertinent as DBA/2 mice exhibit poor conditioned avoidance (Royce 1972) and fail to react to a spatial change of objects in

an open field, thus resembling rats with dorsal lesions of the hippocampus (Ammassari Teule et al 1995). The strain has therefore been proposed as a model of hippocampal dysfunction (Ammassari Teule et al 1995). Studies of dementias and Alzheimer's disease have shown that anti-hypertensive drugs, including angiotensin-converting enzyme inhibitors, have some moderate effects on cognitive decline but that the angiotensin receptor antagonist losartan has a significantly beneficial effect. These findings suggest that manipulation of the renin-angiotensin system may have potential in the prevention, or even reversal, of vascular dementias and Alzheimer's disease (Gard and Rusted 2004). There is now accumulating evidence to suggest that angiotensin IV (AIV), a metabolic breakdown product of angiotensin II, may be the molecule ultimately responsible for the cognition-enhancing effects (Albiston et al 2004). AIV is a six-amino acid peptide that acts via its own AT_4 receptor which has been identified as insulin-regulated amino peptidase (IRAP) (Albiston et al 2001), a ubiquitous enzyme responsible, among other things, for metabolism of important neurochemicals such as oxytocin and vasopressin. AIV inhibits IRAP. The aim of our research was to explore the effects of various novel peptide derivatives of AIV on object recognition in mice of various strains. The effects of the peptides on the memory consolidation/retention component of novel object recognition were determined by subcutaneous administration immediately after the second training trial. Recall was then assessed 24 hours later; thus, drug effects on recall were not assessed. DBA/2 mice are particularly responsive to the cognitive effects of AIV, with BKW and C57 mice showing less consistent improvements. In C57 mice Sar-Ile-angiotensin II was shown to be superior to AIV in that it significantly improved novel object recognition; similarly, Des-His-AIV was shown to be superior to AIV and to significantly improve learning and memory in BKW mice. Comparison of these behavioural results with these effects of these peptides and others on AIV-mediated effects provides interesting insights into the mechanism of action of AIV on cognition and provides a useful starting point for the development of potential therapeutic agents targeted at the AT_4 receptor.

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Oral drug delivery: effective design and *in vivo* validation of modified-release systems

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The utilization of modified-release (MR) technologies for the successful development of orally administered drugs is increasingly important for new chemical entities (NCEs) as well as for traditional product life-cycle management. The US market size alone for oral MR products has recently been estimated at $35 billion with a growth rate of 10% each year. Key drivers for this growth are sub-optimal biopharmaceutical properties for emerging NCEs and a drive to improve patient compliance and clinical outcomes, as well as commercial drivers to ensure product differentiation and maximize brand value in the face of generic incursion and shrinking development pipelines. The choice of potential MR formulation technologies is vast, with numerous strategies available to achieve a wide variety of drug-release profiles. The challenge to the formulation scientist therefore becomes one of selection to ensure desired *in vivo* performance. Traditional formulation approaches utilize available preclinical data, which are typically unrepresentative of performance in humans, or human pharmacokinetic data, which will be limited in early development. There may also be the risk of 'technology push' if a company already has proprietary MR technologies available. It is proposed that the optimal strategy for MR formulation development is focused around the physico-chemical and biopharmaceutical properties of the molecule, in conjunction with human regional bioavailability data. The ability to conduct human drug absorption (HDA) studies by the targeted delivery of drug to specific regions of the gastrointestinal tract allows definitive information to be generated on the optimal site(s) of delivery to achieve the desired pharmacokinetic profile and/or pharmacological response. This knowledge ensures data-driven decision-making in formulation development in terms of drug form, excipient choice and release-rate profile. Identification and validation of the optimal MR formulation can then be achieved *in vivo* through the novel concept of formulation design space in the early clinical development setting. Given the absence of proven *in vitro–in vivo* correlations (IVIVCs) at this stage, there are limitations and risks in restricting the initial MR test system to two to three formulation prototypes based upon *in vitro* characterization data alone. Instead, by configuring and characterizing a range of formulation inputs and performance outputs, a formulation design space can be defined, upon which a regulatory submission can be based. This opens up the possibility of then being able to administer any composition in this framework within a flexible clinical protocol in response to interim pharmacokinetic, pharmacodynamic or scintigraphic data. When used in conjunction with the ability to rapidly manufacture and test drug products (i.e. within a 1 week cycle time), this approach presents a highly efficient way of identifying an optimal MR formulation system within a single clinical protocol in early development. In summary, it is believed that the generation of HDA data to define the preferred formulation strategy, coupled with the ability to rapidly identify an optimal formulation composition in humans through the use of design-space concepts, presents a real opportunity to reduce the time and cost in early development to demonstrate proof-of-concept for MR formulations.

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The application of quality by design to excipient supplies: a customer's perspective

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In September 2004 the US Food and Drug Administration (FDA) published its guidance on *Pharmaceutical cGMPs for the 21st Century – a Risk-Based Approach* and *Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* and more recently, in September 2006, *Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations*, which are fully aligned with the International Conference on Harmonisation (ICH) guidance set out in Q9 'Quality Risk Management' and Q8 'Pharmaceutical Development', pointing towards an expectation that the pharmaceutical industry will take a Quality by Design (QbD), Risk Management approach to the development of drug products. Although excipients are by design biologically inert they may play an important role influencing or even controlling the way in which a drug is delivered. Most excipients are specified by reference to Pharmacopoeial monographs, which are on the whole designed to provide assurance of the identity, purity and microbiological safety, but not functional performance. In some instances a monograph may also include physical property measures related to common applications; these are, however, often quite broad, being designed to include a wide range of different applications and suppliers. QbD and Risk Management require a thorough understanding of the product-manufacturing process, including the active pharmaceutical ingredient and excipients used as raw materials and the nature and pattern of potential variation. In some instances the risk analysis may identify one or more excipients as potentially critical to a drug product Critical Quality Attribute. During the development of a drug product the number of batches of excipient used may be limited and close to the centre of the Pharmacopoeial specification. In QbD terms the knowledge space is smaller than the design space and the control strategy, which is the Pharmacopoeial specification. The objective of QbD is to expand the knowledge space to understand the impact of a wider range of excipient batches within the Pharmacopoeial specification and if necessary set a functional specification/control strategy to provide assurance of the quality and continuity of product supply. To do so it is necessary to work in partnership with the excipient supplier to establish a clear understanding of the nature and pattern of variation of the excipient and to then obtain supplies of excipient at the extremes of the specification so as to be able to stretch the drug product manufacture and performance, and hence expand the knowledge and design space. The very best, twenty-first century excipient suppliers will not only be able to reliably supply material meeting the requirements of Pharmacopoeial monographs, but also information about the nature and extent of the excipient variation, with a stock of material at the extremes of the variation available for customers to stretch the drug-product manufacture and performance. In addition they will, if necessary, be able to work in partnership with the customer to develop innovative tests and controls to ensure reliable drug-product manufacture and performance.

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Current clinical burden and management of neurodegenerative/cognitive decline

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Dementia is a clinical syndrome consisting of a global impairment of cognition. The underlying pathology and associated physiological and psychological signs and symptoms are diverse, and are used to categorize the various forms of dementia. Of these, the most common types are Alzheimer's disease, vascular dementia and dementia with Lewy bodies. In some forms of dementia, for example Alzheimer's disease, memory loss is combined with a general deterioration in the activities of daily living, and frequently behavioural and psychological changes also occur. This

disabling aspect of dementia has a huge impact on the lives of patients and their carers, who in the majority of cases are close family and friends. Dementia has been recognized as a major national and global health issue. It is estimated that 27 million people worldwide are affected by dementia, and its prevalence is set to approach 100 million by 2050. The UK incidence is currently around 700000 (Knapp et al 2007) with this number being set to increase sharply over the next 50 years, bringing with it a huge social care and economic burden. Currently, around 400000 patients with late-onset dementia are cared for by family and friends in the community, with over 200000 patients cared for in residential care homes (Knapp et al 2007). This social care is often intensive, due to the disabling nature of the disease, and for family and friends caring for loved ones with dementia at home, balancing work and caring, becomes increasingly difficult, and many have to give up full-time employment. The loss of income due to carers having to give up employment or reduce their hours is thought to be around £690 million per year. Added to this is the cost of caring for the patient, which is estimated at £16000–37000 per annum per patient depending upon the severity of the dementia (Knapp et al 2007). Current treatment strategies for dementia include the use of acetylcholinesterase inhibitors such as galantamine, donepezil and rivastigmine, and *N*-methyl D-aspartate (NMDA) receptor antagonists such as memantine. Anti-oxidants and anti-inflammatory drugs are also being investigated for their use in this patient population. The cost-effectiveness of these licensed therapies is widely disputed, and the use of these drugs in dementia is restricted by the UK National Institute of Health and Clinical Excellence (NICE 2007). Over the next few years developments in the process of identifying patients with early-stage dementia by novel imaging, biochemical assay or neuropsychometry testing along with the development of drugs which target disease progression or aim to reverse the disease process will prove invaluable if a public health crisis is to be avoided. Much-needed research is also required in the area of addressing either pharmacologically or psychologically the issue of behavioural and psychological changes associated with dementia, and the impact that disease progression has on a patient's ability to carry out activities of daily living.

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Prediction of oral absorption in humans: mathematical models of solubility, dissolution rate, permeability and gastrointestinal transit

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Computational oral absorption simulation is expected to be an effective tool in drug discovery and development. In this presentation, two key mathematical equations for oral absorption simulation, the Noyes–Whitney equation (NWE) and the permeability equation (PE), will be discussed in detail. In the NWE, the diffusion coefficient, hydrodynamics around a particle (particle unstirred water layer (pUWL)) and the solid surface pH should be appropriately calculated from the physico-chemical properties of a drug and the characteristics of the intestinal fluid. When FaSSIF and FeSSIF solubility is used, the diffusion coefficient of bile micelles should be taken into account. In addition, the Henderson–Hasselbalch equation should be modified for FaSSIF and FeSSIF. To calculate the pUWL thickness appropriately, the fluid dynamics model was introduced and compared with the non-fluid dynamics models; that is, the Hintz–Johnson model and the Wang–Flanagan model. Calculation of the relative velocity of a particle against fluid flow from the terminal velocity and the micro-eddy effect will be discussed. Solid surface pH and its impact on oral absorption will be discussed based on the Mooney–Stella equation. In the PE, the effective surface area, effective concentration for permeation and effective permeability (Peff) should be appropriately calculated. The fold/villi structure and flatness of the intestinal tube should be taken into account. A Peff calculation method will be proposed considering the bile–micelle water partition, the membrane unstirred water layer (mUWL) and the transport of bile micelles through mUWL, paracellular pathway, pH and fold/villi structure.

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Polyurethane intravaginal rings for the prevention of HIV transmission

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After more than a decade of work on the development of safe and effective microbicides there has been encouraging progress in the design of microbicide dosage forms, yet significant challenges remain. First, there are potentially several mechanisms for HIV infection and none are well understood. There are also multiple stages of infection, each of which requires distinct therapeutic modes of action of anti-viral agents and potentially site-specific delivery. These factors make the design of dosage forms that deliver the drug in the right place, at the right concentration, and with the right release profile difficult. Second, the majority of the work has been biased towards semi-solid dosage forms, whereas there is a library of other devices that have received less attention, such as suppositories and intravaginal rings. We are developing thermoplastic polyurethane intravaginal rings for the delivery of multiple anti-viral drugs for sustained delivery over 30 days. Results for the sustained delivery of dapivirine and tenofovir will be discussed as well as our efforts to model pharmacokinetics for intravaginal rings.

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Predicting variability in oral drug absorption: using a systems biology approach to integrate information on drug candidates with attributes of an individual patient

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Variability in patient response to the same drug at a given dose (assuming compliance) is a well-known fact. Prescribers deal with such variability by continuous monitoring of treatment outcome or assessing indirect markers of pharmacological effects. However, variable response is also a big obstacle during drug development. The variability in response could be a result of pharmaco-dynamic or pharmacokinetic differences. Pharmacokinetic differences could be related to any of the processes determining absorption, distribution, metabolism and excretion (ADME). Proving clinical benefits (for new drugs) or bioequivalence (for generic products) becomes much harder in the presence of high variability. Thus, understanding the sources of variability and managing them during clinical trials is an inevitable task for all scientists who are involved in drug development. The variations in ADME reflect the interaction of patient characteristics at the time of dose administration with the attributes of each drug/dosage form. *A priori* identification of influential characteristics might improve the design of clinical studies, thereby reducing the likelihood of 'failed' studies due to inappropriate dosing strategies or inappropriate inclusion/exclusion criteria. Although population pharmacokinetics (POPPK) is commonly used to identify patient characteristics that influence ADME, the determination of covariates using POPPK is complicated by bias and competition between multiple variables. The application of POPPK requires data from *in vivo* studies on each specific drug and extending the results to other drugs is not straightforward. In contrast, application of a systems approach for identification and quantification of covariate effects takes account of biological variables already known to be relevant to each step of the processes *prior* to any clinical studies (Rostami-Hodjegan and Tucker 2007). This also avoids many problems with combined effects of multiple covariates. Thus, whereas variable transit time in intestine would have a big impact on variable oral bioavailability for low-permeability and sparingly soluble compounds, it will not affect a highly permeable and highly soluble drug. Examples of variable effect of the same covariate on apparently similar drugs can be demonstrated by expected variable effects of coeliac disease on absorption of compounds from the gut wall. Whereas the lower level of gut-wall CYP3A in coeliac patients is expected to lead to increased bioavailability of CYP3A substrate, the effect will depend on permeability of the compound (i.e. highly permeable drugs may not have significant gut-wall metabolism). Moreover, the reduced transit time in intestine in coeliac disease may counterbalance any increased bioavailability that happens via reduced gut-wall metabolism, as compounds with low solubility or low permeability require longer residence in the gut for complete bioavailability. Increased computing power in recent years has provided the opportunity of building highly complex models of virtual populations using mechanistic, physiologically based pharmacokinetic models incorporating known variability in demographic and biological (genetic and environmental) components and linking them to drug-specific physico-chemical properties (e.g. aqueous and lipid solubility) and *in vitro* data on absorption, metabolism and transport. The covariate relationships embedded in such models are difficult to resolve by simple linear covariate analysis done in POPPK types of analysis. Moreover, the systems approach maximizes the value of all prior *in vitro* information generated during drug discovery and pre-clinical development such that every *in vivo* pharmaco-kinetics study becomes confirmatory rather than exploratory. So the question of variability is not whether we can predict *all* the variability in response, but whether we use *all* our prior knowledge of the system to identify the variable response that we should have known about.

Rostami-Hodjegan, A., Tucker, G. T. (2007) *Nat. Rev. Drug Dev.* **6**: 140–148

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Delivery of siRNA: challenges and oppportunities

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RNA interference (RNAi) has emerged as a powerful tool for suppressing gene expression, thus offering the exciting potential to create novel therapeutics for the treatment of a range of disease states. To date, the production of effective non-viral delivery vectors has been the major challenge limiting the success of nucleic acid-based drugs in clinical trials. The difficulties associated with small interfering RNA (siRNA) delivery include cellular uptake and intracellular activity, instability in serum, degradation by RNase and the requirement for cell-specific targeting. The ideal delivery construct should have the following properties: it should bind to and form self-assemblies with the siRNA to produce nanosized particle/vesicles, allow for repeat dosing without the risk of immune reactions, be charge neutral and non-toxic, be stable under physiological conditions and achieve efficient targeted delivery. The design and application of modified cyclodextrins (CDs) as non-viral vectors provide the opportunity to overcome the barriers to siRNA delivery, both *in vitro* and *in vivo*. CDs are cyclic oligosaccharides composed of glucose units. They are relatively simple and inexpensive, and are well-accepted non-toxic excipients in more conventional drug-delivery systems. CDs are relatively large oligomers and can act as molecular scaffolds on to which a range of functional groups including cell-specific targeting ligands can be grafted. Modified CDs synthesized by our group can form vesicles or artificial liposomes. Vesicle-forming CDs are a major advance on previous classes of CDs and are capable of encapsulating even large polar drugs within their aqueous vesicle interior. In addition, polycationic examples of these CDs, through electrostatic interactions, condense RNA into nanoparticles for efficient cellular transfer. The presentation will review progress to date with the CD vectors relative to alternative technologies.

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Creating novel drug-delivery devices using supercritical carbon dioxide

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This lecture will describe work at Nottingham towards the exploitation of the unique properties of supercritical carbon dioxide ($scCO_2$) for the preparation of novel polymer composites for drug-delivery applications. Supercritical fluids provide a unique combination of gas-like and liquid-like properties, allowing processing that could not be performed in conventional solvents. Moreover, $scCO_2$ is inexpensive and provides an environmentally acceptable alternative to the use of conventional organic solvents. $scCO_2$ plasticizes certain amorphous polymers, effectively liquefying them at close to ambient temperature. Under these conditions it is possible to physically mix active growth factors and even live mammalian cells within the liquefied polymer phase. Following depressurization, microporous foams are generated, leading to trapping and encapsulation. By varying the depressurization rate, the pore size within these foams can be controlled. No solvent residues remain after processing and high protein loadings can be incorporated into scaffolds in a one-step process. Examples from Critical Pharmaceuticals of microspheres created by the same supercritical processing route will be discussed, with particular reference to the preparation of drug-delivery devices for delicate protein-based therapeutics such as human growth hormone.

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Coronary stents: the past, present and future

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Coronary stents are used in the treatment of coronary artery disease to restore blood flow within the coronary artery and reduce the likelihood that the vessel will become blocked over time. The stent is placed in the coronary artery via a catheter and a minimally invasive clinical procedure. Coronary stent technologies have evolved significantly since their introduction in the 1990s (Palmaz 2003). The first-generation stent designs have subsequently been replaced with newer technologies and materials. The combination of the coronary stent coated with an active pharmaceutical compound has given rise to the drug-eluting stent. The mechanical property of the stent device combined with the pharmaceutical properties of the drug coating has increased the effectiveness against re-blocking or restenosis within the coronary artery (Moses et al 2003, Stone et al 2004). This combination drug/device product has revolutionized coronary stenting over the past 5 years and the annual worldwide drug-eluting coronary stent market is now estimated in the region of US$4 billion (see Medtech Reports, www.medtech-reports.com/drug-eluting-stents-market). More recently uncertainties over the use of drug-eluting stents and the risk of late stent thrombosis have been published (Lagerqvist et al 2007, Stone et al 2007). The future design of drug-eluting coronary stents is likely to take into account mechanical advancements in stent and catheter technologies as well as enhancements to the drug-delivery technologies associated with drug-eluting stents.

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Orthopaedic bone cements: drug–device combination

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Disease conditions such as osteoarthritis, osteoporosis or rheumatoid arthritis cause degeneration of the joint. Total joint replacement has been widely adopted to treat these debilitating illnesses, as it is often the only course of treatment to alleviate pain and improve the quality of life. The number of joint replacements worldwide is rising and is expected to continue to do so, given the increase in population of the elderly and associated disease and trauma. The success and widespread use of joint replacements in the management of arthritic conditions and trauma have made a significant impact in modern healthcare. Bone cements have been traditionally used in placing hip and knee joints, where they fill the space between the implant and the joint. Surgeons replace a dysfunctional joint using metal alloys and polymeric materials, with a functional, long-lasting prosthesis. Acrylic bone cement based on poly(methyl methacrylate) was first used in the late 1960s by Sir John Charnley in the UK and is extensively used worldwide today. Infection is often a complication following joint replacement surgery and the use of antibiotic-impregnated cements is emerging to be a potentially effective clinical procedure that may assist in reducing the incidence of deep infection. The main advantage of local antibiotic delivery is the ability to achieve high levels of antibiotic at the target site without increasing systemic toxicity. An emerging trend in clinical medicine is the use of combination devices and the bone cement is being exploited as a potential drug carrier. The first part of the presentation will highlight the inclusion of antibiotics and additives in bone cements that may decrease the incidence of infection, promote bone healing or decrease bone resorption and its efficacy as a drug-delivery vehicle. The second and final part of the paper will focus on the tissue-engineering techniques combined with specific local cancer treatments that may be an excellent alternative to restore large bone defects that occur, for example, after tumour resection. Tissue engineering /regenerative medicine is an emerging multidisciplinary field that is likely to revolutionize and improve the health and quality of life by restoring, maintaining or enhancing tissue and organ function. The tissue engineering approach to repairing bone defects has been to combine cells capable of osteogenic activity with an appropriate scaffold material to stimulate bone regeneration and repair; however, bone implants often fail to integrate successfully to the host due to delayed vascularization. Thus, the targeted delivery of stem cells, growth factors and therapeutic agents from a scaffold material so that they can be released locally at the site is an approach that is being researched extensively in our laboratories. This presentation will also highlight the development of some innovative bioactive scaffolds based on composites, and also explores the possibility of combining loading polymer-tethered bioactive ceramic porous substrates with anti-cancer agents to achieve targeted delivery and reduce systemic side effects of treatment.

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Psychological assessment of neurodegeneration/cognition in the elderly

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Psychological theory and associated models must play a major role both in the assessment of cognitive change in older adults, and in the assessment of efficacy of interventions aimed at redressing these changes. Psychological approaches are concerned with detailed modelling of the cognitive processes that determine everyday functioning, including motivation, mood, social behaviour, activities of daily living and day-to-day functioning (Gray and Della Sala 2004). They provide a framework for delivering a precise and individual picture of cognitive

competence. Considering the increasing age profile of our population, maintaining cognitive competence has to be prioritized, first to encourage successful ageing and independent living, and second to reduce the experience of 'burden' and stress that such changes naturally induce in older people and in their families (Moniz-Cook and Rusted 2004). Aspects of cognitive ageing that impact most directly on functional independence include changes in attention, executive function, working memory and prospective memory (Salthouse et al 2005). I will present examples, from work in my laboratory, that demonstrate how we measure cognitive change in the key areas of attention and memory, and how we explore potential modulators of these changes. The paper will conclude with consideration of the link between current psychological models and clinical needs in relation to emerging candidates for pharmacological intervention in age-related cognitive change.

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Modification of the bacterial phenotype: a strategy to preserve our anti-bacterial arsenal

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The intensive use of bactericidal and bacteriostatic antibiotics has applied enormous selective pressure on populations of pathogenic and opportunistic bacteria and has led directly to the emergence of multi-drug resistant genotypes that threaten our capacity to effectively treat many infectious diseases. The development of therapeutic agents that do not kill pathogens but 'disarm' them by removing or inhibiting the expression of virulence factors and antibiotic resistance determinants essential for the survival of the bacterium at the site of infection may reduce the propensity for the selection of resistant forms. Two examples of modification of the bacterial phenotype as a therapeutic paradigm will be described. *Escherichia coli* K1 isolates synthesize a polysialic acid (polySia) capsule, are components of the adult gastrointestinal microbiota and may cause lethal bacteraemia and meningitis if acquired maternally by newborn infants. We used a neonatal rat pup K1 infection model to establish that prompt administration of a selective capsule depolymerase reverses the bacteraemic state and prevents death of almost all pups. Thus, a single, low intraperitoneal dose of recombinant endoneuraminidase E administered 1 day after oral infection strips the protective polySia capsule from bacteria during the blood phase of the infection and interrupts transit to the meninges via the choroid plexus and blood–brain barrier. In the context of Gram-positive infections, we are able to modulate the susceptibility of methicillin-resistant *Staphylococcus aureus* (MRSA) clinical isolates to second- and third-generation β-lactam agents using naturally occurring galloylated polyphenols such as (−)-epicatechin gallate (ECg). ECg interacts in non-lethal fashion with the staphylococcal cytoplasmic membrane (CM) and elicits phenotypic changes to the cell wall, resulting in large reductions in susceptibility to oxacillin and other β-lactams. Changes to the physical properties of the CM also prevent the secretion of a range of extracellular proteins associated with the virulence of MRSA. Barriers to the development of these molecules as therapeutic agents will be discussed.

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Demonstration of therapeutic equivalence for generic (hybrid) inhalation medicines in Europe

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Orally inhaled products (OIPs) are often approved with posologies that correspond to the upper part of the dose–response curve. This, in combination with the fact that dose–response curves for OIPs in general are quite flat, has so far received little attention in the development and assessment of generic versions (in Europe termed hybrids). As a consequence, some hybrids have been approved on the basis of pharmacodynamic studies with a single – often high – dose level. Due to the obvious lack of sensitivity such studies are likely to conclude equivalence even though the hybrid may in fact have some clinically relevant differences from the originator. The European guidance is therefore being changed accordingly. It is recommended that companies adopt a stepwise strategy towards the demonstration of therapeutic equivalence. The sequence should be (1) *in vitro* evaluation, (2) pulmonary deposition, (3) pharmacodynamic comparison and (4) a full phase III study. With this approach a hybrid product can potentially be approved as soon as one of the steps has demonstrated a sufficient level of similarity between the hybrid product and its originator, and it is thus not necessary to go through all steps. This means that European agencies are opening up for approval of generic/hybrid OIPs solely on the basis of *in vitro* data. This talk introduces the stepwise approach towards demonstration of therapeutic equivalence in more detail regarding the technical requirements and discussed differences between drug classes, asthma versus chronic obstructive pulmonary disease, and adults versus children. The main focus is the demonstration of sensitivity in pharmacodynamic studies. Most importantly, regulators will expect such studies to include (at least) two dose levels of both the hybrid and the originator product and that the demonstration of sensitivity is assured by showing a statistically significant difference in effect at the two dose levels.

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Pharmacogenetics: a regulatory perspective

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The science of pharmacogenetics has been developing steadily in recent years, although the clinical applications are still limited and, as yet, there are few examples of regulation-based genetic findings. What examples have made a regulatory impact? What can we learn from these? What future directions are important to widen this impact? These questions are explored further. Pharmacogenetics is defined in terms of DNA sequence variation relating to pharmacokinetics or pharmacodynamics that can influence clinical response. Some regulatory guidance on exploring pharmacogenetic issues during drug development has been developed in recent years, and particularly focuses on the need for preclinical and phase I/II studies to examine the influence of genetics on pharmacokinetic variation, interactions and dose–response. However, the impact of this research has so far been limited, and phase III trials typically involve a single dosing strategy for all patients, regardless of genetic variation. Phase III studies offer further scope for genetic investigation, particularly in relation to non-responders, and pharmacokinetic outliers. Hypotheses generated from such work could be prospectively examined in Risk Management Plans, which are now mandatory at the time of licensing in Europe. European regulatory guidance on scientific issues during development is offered by the Pharmacogenomics Working Party of the CHMP. This is a multidisciplinary group that advises on a case-by-case basis. Issues to date have typically related to oncology, central nervous system and immunology products, and include biomarker validation, labelling, diagnostics/testing issues and clinical trial design issues. In relation to minimizing the risk of adverse reactions, most emphasis has centred on single gene variation affecting drug-metabolizing enzymes. Among the well-characterized examples, cytochrome P450 2D6 (CYP2D6) and thiopurine–S-methyl transferase (TPMT) provide good illustrations of the potential value and limitations of this approach. Studying the influence of multiple genes, particularly when combined with the influence of non-genetic factors, could greatly increase the clinical applicability of pharmacogenetic research, and lead to more options for regulatory action. Such an approach is being researched in an attempt to reduce haemorrhagic reactions associated with warfarin. Recent prospective research has shown the value of exploring pharmacodynamic variability, in particular the influence of human leucocyte antigens (HLAs), and the risk of serious immune-mediated adverse drug reactions (e.g. with abacavir and carbamazepine). The impressive predictive value of testing some populations of patients may now result in regulatory action with firm recommendations for HLA testing before treatment, and this area of research therefore shows great potential. Advances and increasing commercial viability of genetic testing technology importantly sit alongside the recent pharmacological research. Further development (e.g. in near-patient testing options), validated phenotyping and regulatory oversight will be important if pharmacogenetics is to find widespread uses. From a regulatory perspective, there is scope for pharmacogenetics to play an increasing role in drug development and post-marketing pharmacovigilance activities, with the aim of optimizing dose regimens, patient selection and risk minimization. However, significant progress will require more prospective research and co-ordinated strategies involving regulators, industry and academia.

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Solid dispersion technology

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The ability of pharmaceutical solid dispersions to enhance the oral bioavailability of poorly water-soluble drugs was described by Seguichi and Obi (1961) over 4 decades ago [1]. Achieving adequate oral bioavailability for poorly water-soluble drug candidates is a major challenge for the pharmaceutical industry. The number of poorly water-soluble drug candidates has increased substantially in recent years due to the advancements in high throughput screening during the drug discovery phase. Solid dispersion technology is one of the formulation stategies available to increase the oral bioavailability of these poorly water-soluble drug candidates. The increased dissolution and hence bioavailability of a drug from a solid dispersion in some circumstances is due to the generation of a metastable high energy form of the drug during preparation. Whilst the high energy form results in advantageous higher aqueous solubility, it is inherently unstable. The time frame for conversion to a lower energy form of the drug can vary from days to years depending on a wide range of factors including choice of carrier, method of preparation and storage conditions. Concern surrounding the physical stability of solid dispersion dosage forms has limited the widespread commercial application of this technology. The consequences of the drug solid state form altering post registration were highlighted with the temporary withdrawal of Ritonavir capsules from the market 2 years after their launch (Morissette et al 2003). The aim of this talk is to highlight advances in understanding of solid dispersion behaviour both solubility and stability. Initially, a brief introduction will be given to the formulation challenges presented by poorly water-soluble drugs for oral delivery and the potential of solid dispersion technology to address these challenges. The various classifications of solid dispersion systems will be explained. The wide range of carrier material that can be used to optimise the dissolution and the stability of these solid dispersions will be discussed. Examples of the impact of preparation techniques on solid dispersion behaviour will be given. The wide range of analytical techniques available to study the solid state of these systems will be highlighted throughout the talk.

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Development of food waste products as novel excipients

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Waste generated by the food and drink industry amounts to 12.6 million tonnes per year, which is more than 10% of the total waste produced in the UK. Consequently there is a growing issue as the cost of disposing of waste in landfill significantly increases. Hence the food and drink industry is examining ways to exploit these ‘co-products/by-products’. Interest and research are slowly growing to investigate such components with a view to adding value to co-product streams by exploiting them for high value uses such as pharmaceuticals. Food waste covers a broad spectrum ranging from animal to plant. In this paper, waste derived from the produdion of sugar, the manufacturing of beverages and the production of starch and its derivatives using cereal grains is mainly discussed. All these materials comprise macromolecules which are polymeric in nature and could pave the way to design novel excipients in pharmacy. Today a limited range of these biopolymers is already included in pharmaceutical formulations, namely peptic polysaccharides originating from apple pomace and citrus pulp. However, progress is required to further explore other biopolymers and fully utilise them as excipients. Polysaccharides and storage proteins found in the plant cell wall and endosperm tissue of cereal seeds, respectively, will be reviewed with emphasis on the biological and chemical properties of these macromolecules. Two materials are chosen to illustrate the potential applications of food waste as excipients: zeins and hemicellulosic polysaccharides. Zeins, which are storage proteins from maize grains, originate fom starch manufacture. When included as a major component in oral controlled release systems or used in films as topical sustained-release drug delivery devices, results demonstrated that they can be successfully used as pharmaceutical excipients. Hemicellulosic polysaccharides located in the cell wall of cereal grains which derive from brewery and distillery co-products show gel forming properties. Production of hydrogels with the inclusion of model drug was achieved and showed some promise as a drug delivery device. In conclusion, food waste contains a significant amount of biopolymeric material which can be included as excipients. However, further work is required to fully explore this diverse source of novel excipients.