ging. Computer-based learning (CBL) is well established and its benefits are widely reported. With recent studies showing the Web to be a useful medium for learning and assessment (Yazon et al 2002), the aim of this study was to produce a web-based tutorial for undergraduate MPharm students. For the aim to be fulfilled, the following objectives were set: to identify undergraduate MPharm students' weaknesses in their understanding of the acid-base equilibrium course; to identify students' attitudes towards web-based learning aimed at pharmaceutics; to design a web-based tutorial on acid-base equilibrium; and to assess whether students benefited from the web-based tutorial. The student learning experience was measured through questionnaire analysis. Questionnaires were given to students before (n = 86) and after the tutorial (n = 58) to assess student attitudes towards the tutorial as a supplement to a lecture course. Students generally had a positive attitude towards CAL/web-based tutorials and indicated that the tutorial would be a good supplement to the current lectures (89.5%). The aspects of the acid-base equilibrium course that the students found most difficult to understand were the Bronsted-Lowry theory (75.8%) and performing calculations based on acid-base theory (82.6%). The content of the tutorial was determined by the students' responses and concentrated, in particular, on the areas that students were finding difficult to understand, interpret and apply. Increase in performance or effectiveness using CBL is strongly influenced by the design of the interface in the computer-based materials (Evans et al 2004). If the potential of computer-based delivery is to be realised, usability and interactivity of the interface between the student and the courseware has to be considered and should not be used simply as an extension of the chalkboard, putting lecture notes directly on the web. The tutorial therefore contained theory, written by an undergraduate student to address the needs of the student cohort. The theory was then required to be applied to solve calculation-based self-assessment questions. It was designed for use on WebCT, an interface familiar to the students and piloted to a small group to identify any navigational and design issues. Students accessed the web-tutorial with minimum help and instruction thus it would be suitable for self study. Students responded that the tutorial did help their understanding of the subject area (77.6%) and addressed material that was difficult to understand from a lecture course (81.0%). Although it was felt that the tutorial addressed similar learning needs as the lecture course (75.9%), it was thought that the tutorial was an effective supplement to the lecture course (82.8%).

Yazon J. O. et al (2002) *Computers and Education* **38**: 267–285
Evans, C. et al (2004) *Computers and Education* **43**: 49–61

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Design a web-based learning pH-partition package

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The dominating factors that affect absorption of weak acids and bases are pH at the absorption site and the lipid solubility of the unionised species. Student examination performance and course review questionnaires have highlighted this as an area that could benefit from additional support supplementary to the lecture course. A computer-based learning (CBL) package may be used to address this need. Many online courses, however, consist merely of a series of textual notes and pictures with little navigational information or choice. A recent study by Evans et al (2004) highlighted errors in usability of computer-bases learning systems and included: not structuring material to more than one level; not "chunking" information; not providing sufficient navigational information; providing either too little or too much navigational choice; and not providing interactions and self-assessment questions. Therefore, a Computer Aided Learning (CAL) package was created to support the lecture series and the needs of the students. In this endeavour two focus groups (n = 8) were conducted, the former to develop the CAL package and the latter to evaluate it. The initial focus group used a theme plan with questions concerning CAL and the pH-partition hypothesis to explore the views and ideas of the students that had recently completed the lecture course. Discussions within the focus group were recorded and the results showed that students wanted a bright, interactive and relevant learning aid to complement the lectures. They wanted to be able to work at their own pace and to be able to test their understanding throughout. The package was created using Microsoft PowerPoint. It was designed to incorporate animation, hyperlinks and to be interactive. An evaluation focus group and semi-structured interviews were used to determine whether the package met the needs of the students. Key elements identified by the focus group as desirable in the package were the use of bright, animated graphics and summary pages. The benefits of being able to work at one's own pace and to assess knowledge through questions built into the package, identified by the initial focus group as important criteria, were also viewed as being successfully addressed by the package. The degree of success of CAL packages will depend on how closely they fit with the needs of the students, the course and the lecturer. The students believed the package to be excellent, with colour, animation and self-assessment questions that met the identified needs.

Evans, C. et al (2004) *Computers and Education* **43**: 49–61

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Differentiating inquisitive and acquisitive learning: a comparative study at the Portsmouth and Brighton schools of pharmacy

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Educational research has highlighted the relative benefits of providing students with complete and partial sets of notes, indicating that students are potentially inconsistent or even inexperienced note-takers (Kiewra et al 1988). It was noted that reviewing a complete set of notes for a sufficient amount of time resulted in a better test performance than reviewing personal notes alone. However, the best test performances were achieved when a combination of personal notes and provided handouts were used. This was attributed to the importance of personal cues generated during the note taking process. These personal cues are more likely to be recalled by the student than those suggested by the lecturer. "Skeletal" notes are based on complete notes, but are deliberately incomplete. They contain the structure and the detail of the complete notes, but also allow the student to incorporate personal cues and hence maximise the encoding function. It was the aim of this study to assess staff and student attitudes to different resource provision at the Portsmouth and Brighton Schools of Pharmacy, and to ultimately determine whether the nature and type of resource provision could affect academic performance. Staff and student attitudes were assessed via a questionnaire based on that piloted previously (Ingram et al 2004). The questionnaire was developed after the method of McLennan & Isaacs (2002), which assessed the role of handouts and course delivery in veterinary science lectures at the University of Queensland. The final questionnaire was developed after a pilot scale study, and analysis by focus groups in both institutions. Results indicated that students and staff differ comprehensively in their opinions regarding the supply, usage and nature of handouts, with lecturers preferring to make use of partial handouts when they see a need. Students, on the other hand, show a preference for as many detailed handouts as possible. Staff and students did share the same generalised view that handouts encourage learning. However, students as a whole believe that handouts do not discourage further study in a subject, and also do not discourage attendance to lectures. Demographic factors that were shown to have an effect on responses were language (particularly where English was not the first language), year of study, choice of pre-registration placement, gender, marital status, age and the number of children.

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Kiewra et al (1988) *J. Ed. Psych.* **80**: 595–597
McLennan, Isaacs (2002) *Aust. Vet. J.* **80**: 626–629

Invited Abstracts

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Predicting drug absorption and disposition: transporter, solubility and elimination interplay

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The Biopharmaceutics Classification System (BCS) was developed to allow prediction of in vivo pharmacokinetic performance of drug products from measurements of permeability (determined as the extent of oral absorption) and solubility (determined for the highest dose strength in 250 ml of water over the pH range 1–6.8). Although the BCS is useful for characterizing drugs in Class 1 (high permeability; high solubility) for which drug dosage form dissolution alone may be amenable for waiver of in vivo bioequivalence studies, there is little predictability concerning drugs in Classes 2 (high permeability; low solubility), 3 (low permeability; high solubility) and 4 (low permeability; low solubility). Early this year (Benete et al 2005), we suggested that a modified version of such a classification system, designated the Biopharmaceutics Drug Disposition Classification System (BDDCS), may be

useful in predicting overall drug disposition including: routes of drug elimination; the effects of efflux and absorptive transporters on oral drug absorption; when transporter-enzyme interplay will yield clinically significant effects (e.g., low bioavailability and drug-drug interactions); the direction, mechanism and importance of food effects; and transporter effects on post-absorptive systemic drug concentrations following oral and intravenous dosing. These predictions are supported by a series of studies from our laboratory over the past few years investigating the effect of transporter inhibition and induction on drug metabolism. In BDDCS, Classes 1 and 2 drugs are predominantly eliminated by metabolism, while Classes 3 and 4 drugs are predominantly eliminated unchanged via urinary or biliary excretion. Transporter effects will be negligible for Class 1 compounds. Efflux transporter effects will predominate in predicting the oral exposure of Class 2 compounds, while absorptive transporters will have a major influence on the oral exposure of Class 3 compounds. Transporter-enzyme interplay in both the intestine and the liver will play a major role following oral dosing of Class 2 compounds, and hepatic uptake transporters can also be very important for such drugs. We conclude by suggesting that the BDDCS, using elimination and solubility criteria, may provide predictability of drug disposition profiles for all classes of compounds.

Benete, L. et al (2005) *Pharm. Res*. **22**: 13–22

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Obesity: why a big issue? Overview of the public health programme

P. Mason

Obesity is now recognised as a major public health programme in the UK, posing a threat second only to smoking. In England, 22% of men and 23% of women were obese (BMI $\geq$ 30 kg/m^2) in 2002 and the prevalence is increasing steadily. The ill health linked to obesity is considerable. For example, obese women are thirteen times more likely to develop type 2 diabetes than non-obese women. The economic costs of obesity in England have been estimated as approximately £3.7 billion a year and if overweight is included the costs double. A weight loss of 5–10% body weight in obese individuals is associated with significant health benefits, particularly in a reduction in blood pressure and reduced risk of developing type 2 diabetes and cardiovascular disease. Recent reviews have shown that a low energy diet, together with increased physical activity and behavioural support can achieve beneficial amounts of weight loss, at least in the short term, though maintenance of weight loss beyond the first year is difficult. Community pharmacy provides a potentially ideal setting for weight management intervention of adults. Contact rates with the local population are high and community pharmacists are potentially well placed to detect and manage obesity in high risk patients. However, obesity is difficult to tackle. It is a complex, chronic condition that can only be managed effectively through lifelong care. It requires knowledge and skills, thorough assessment of the individual with management tailored to the individual. Because of these complexities and the potentially enormous caseload, health professionals and patients often lose heart and stop trying. To overcome these barriers, there is a need for clear guidelines on case selection, intervention and referral, expanded community dietetics and exercise referral services, effective training and support materials and further research to identify approaches which work. A number of new developments such as dedicated weight management programmes in pharmacies and GP surgeries, referral to commercial slimming organisations and establishment of clear clinical pathways show promise for weight management and obesity treatment.

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Public health impact of obesity

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Obesity is one part of the picture of weight gain experienced across most of the population. In the developed countries the impact was felt first in the USA and then it increasingly spread across Europe, with the highest rates of child obesity in countries (Greece and Italy) formerly thought to be protected by the 'Mediterranean diet'. There are multiple models of explanation, which will be presented. The leading view is that obesity cannot be explained by individual factors but requires an ecological form of analysis based upon changing diet, urbanisation and post-industrial patterns of culture, work and leisure. By implication, the task of reversing the determinants of population weight gain will be difficult, to say the least. Experience in the USA suggest that the medicalisation of obesity results in higher healthcare and societal costs – now matching smoking – but only has limited success. The World Health Organisation has devised its Global Strategy for Diet, Physical Activity and Health and in England an obesity strategy forms part of the Choosing Health. Obesity – in the context of associated dietary and lifestyle diseases – will be a major feature of health trends into the future and, because of its socio-demographic profiles, a major cause of health inequalities. Pharmacists, like other health professions, will have a role to play.

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New opportunities in solid state characterization

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New opportunities in solid state characterization exist because it is now possible to control the release rate of formulations by controlling the solid form. In addition to salts, cocrystals and amorphous forms can be used to alter dissolution rate. Because of this it is important to characterize and control the solid form. Additionally, the mechanical properties and the stability of the material can be varied by varying the form. Solid state characterization also provides opportunities to rapidly progress compounds from candidacy to IND. The approach involves "front loading" as many characterization studies as possible to reduce problems later. The strategy involves finding the best solid form for manufacture and the development of a manufacturing process and formulation that preserves this form. If necessary, salts or cocrystals are developed early to solve solubility problems. PAT and quality by design are among the main components of the strategy. Sophisticated characterization techniques, such as solid state NMR spectroscopy, are used to verify the noninteracting nature of the formulation. Emerging predictive strategies are also of great interest. Ultimately, this strategy will reduce time to market and reduce risk of failure especially in the early (IND) stages of industrialization.

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Polymorphism and crystallinity of pharmaceutical compounds: investigations using spectroscopic techniques

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Among the many challenges in the development of drugs from pure compounds to dosage forms, suitable for safe and efficacious use in patients, increasingly important problems are crystalline polymorphism and poor aqueous solubility of many small molecular weight drugs. With the advent of combinatorial chemistry these problems are likely to become even bigger in the future. Investigation of the polymorphism of pure drugs and drugs in dosage forms is therefore an area of intensive research both in the pharmaceutical industry and in academia. A lack of knowledge about the polymorphism of drugs may have severe consequences not only for efficacy and safety of drugs, but also for patenting of drugs and registration of dosage forms. To increase the solubility of drugs, and thus their bioavailability, crystalline drugs may be converted to amorphous forms, either on their own or together with polymeric excipients. Lack of knowledge about the physical stability of these systems is a major obstacle in the rational development of such dosage forms. To be able to tackle the problem of polymorphism and to be able to formulate drugs in the amorphous state, it is of great importance to rapidly and reliably detect and quantify the solid state properties (crystallinity, polymorphism) of drugs, both alone and in pharmaceutical dosage forms. Currently x-ray diffraction and thermal analysis are mainly used to investigate these properties. The aim of this presentation is to investigate the use of a range of spectroscopic techniques, to perform qualitative and quantitative analysis of the solid state properties of drugs alone and in pharmaceutical dosage forms, in which the drug is present in different solid state forms. Research from our group (Forster et al 2003a, b; Strachan et al 2004a, b, c, 2005) will be presented, covering the use of Raman spectroscopy, terahertz spectroscopy and second harmonic generation in the above-mentioned areas.

Forster, A. et al (2003a) *Pharmazie* **58**: 761–762
Forster, A. et al (2003b) *Pharmazie* **58**: 838–839
Strachan, C. J. et al (2004a) *J. Raman Spec*. **35**: 347–352
Strachan, C. J. et al (2004b) *J. Raman Spec*. **35**: 401–408
Strachan, C. J. et al (2004c) *J. Pharm. Sci*. **93**: 733–742
Strachan, C. J. et al (2005) *J. Pharm. Sci*. **94**: 837–846

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Molecular profiling using microarrays

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The increasing availability of genomic data is rapidly changing drug discovery and validation and the assessment of efficacy and toxicity of compounds. Thus, molecular profiling is a combination or individual application of mRNA expression, proteomic or metabolomic measurements that characterize the state of a cell or tissue or an organism and information from genomic, proteomic and metabolomic measurements are used to identify new drug targets, to develop novel diagnostics and to pre-select patients likely to benefit from a distinct therapy. We apply mRNA expression profiling with DNA microarrays in different areas, to characterize the activity of bioactive compounds, to characterize states of diseases in patients and to study model systems like exercise-induced stress. Low-medium density arrays are used to investigate the effect of synthetic agents on transcription in selected cell lines. Examples are given summarizing the biological activity of synthetic sphingolipids and of agents interfering with sphingolipid metabolism. Criteria for the diagnosis of the Systemic Inflammatory Response Syndrome (SIRS) or sepsis do not reflect molecular details. We apply microarray mRNA analysis to test the hypothesis that single genes or combinations of genes are differentially expressed between patients with severe sepsis/septic shock and patients with SIRS and also in patients with organ dysfunction/shock without clinical signs of infection, to deduce molecular signatures and regulatory networks and thus to classify patients. A medium density microarray with 5000 pre-selected probes was used and gene expression data of white blood cells of more than a thousand patients were analysed. We present gene activities that may be specific to patients with sepsis and septic shock and transcription profiles that could be used to distinguish between infectious and non-infectious sepsis. Optimized cluster analysis methods, together with non-linear correlation analysis methods, were used to extract hypotheses on gene regulatory networks from transcriptome data, model data are correlated with clinical data. However, disease-related functions of genes gives must be followed up with other studies that test individual hypotheses about gene function. Taken together, these data provide evidence that an assessment of differential gene expression by microarray technology will afford clinically relevant improvements of sepsis diagnosis in the future. Furthermore, we have investigated transcriptional changes induced by physical exercise. Healthy male subjects underwent treadmill exercise for two hours and transcription was analysed in whole blood before, during and after the exercise. Changes in gene activities were found which may provide further insight into the molecular mechanisms of exercise induced asthma.

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Characterisation of modified release products using novel analytical techniques

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In light of the FDA guidance for implementing a comprehensive quality system model for manufacturing human and veterinary drugs, there has been increased activity in the pharmaceutical industry around better understanding of pharmaceutical products. The "Quality by Design" philosophy requires that quality be built in from the outset and continue throughout the product' development lifecycle. To achieve "Quality by Design" it is necessary to identify and assess the key quality attributes and process parameters for the manufacturing process. There are many assessment tools available, including FMEA (failure mode effects analysis) and the outputs are used to prioritise activity design to gain better process understanding. This can be achieved in a variety of ways, among which the most extensively applied are Design of Experiments and PAT technology. A variety of technologies can be applied to modified release products to address the specific challenges encountered with these systems, which include osmotic pump tablets and multi-particulates in capsules. Chemical imaging has been used to better understand unexpected dissolution results for multi-particulate beads and to demonstrate effects of different manufacturing processes on osmotic pump tablets. X-ray microtomography provides a means of assessing the overall structure of a modified release product. Images can be collected during dissolution experiments to provide clear mechanistic evidence for the profile produced. Different approaches to monitoring coating processes using Near-Infrared Spectroscopy have been tested and compared. Good correlations between NIR reflectance spectra and weight gain, coat thickness and drug release performance have been demonstrated. This increased understanding of the coating manufacturing step is key, since in many cases dissolution performance is controlled by a functional or active coating. The information provided by the wide range of technologies described here provides increased process understanding for a number of different aspects of modified release product manufacture. Emerging technologies will increasingly be applied on- and at-line, to provide real time information during manufacture.

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Analytical considerations in the dissolution testing of oral modified release products

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The development of dissolution tests for oral modified release products requires careful consideration. These products have unique properties compared with immediate release dosage forms and require the pharmaceutical scientist to carefully consider the objective and design of the test method. The data generated from the dissolution test must be meaningful and the methodology should be practical. This presentation will consider both of these aspects of dissolution test design and application. There are several reasons for performing dissolution testing. In development, it can be used as a tool to evaluate biological performance of a dosage form as part of an in vivo/in vitro correlation. The dissolution test can be used to predict or model the drug release in the gastrointestinal lumen, necessary to achieve therapeutic levels of drug in the pharmacokinetic compartment. In manufacturing, the test is used to indicate that control of the release profile of the dosage form under described dissolution conditions satisfies specifications that have been agreed with regulatory agencies. This latter requirement addresses safety and efficacy considerations (e.g. dose dumping or delivering drug to the site of absorption). The development of meaningful specifications that meet regulatory approval will be discussed. The practical application of dissolution testing will be outlined. Dissolution systems and analytical technologies employed to generate data collected over an extended period of time will be compared, discussed and the relative merits assessed. Case studies of dissolution testing of several modified release products will be provided, detailing challenges associated with features of their design, and pitfalls to consider when developing such a test.

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Neural grafting for Parkinson's disease: what? where? when and in whom?

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Parkinson's disease is a chronic neurodegenerative disorder of the central nervous system which is characterised by the loss of dopaminergic neurons and their projection from the substantia nigra in the brainstem to the striatum. This loss of dopaminergic cells leads classically to a movement disorder characterised by tremor, rigidity and bradykinesia. As a result of this localised pathological loss of cells within the brain, therapeutic treatments are available which target this network. Thus, effective drug treatments exist in the early stages of Parkinson's disease but with time these become less effective and produce their own side effects. As a result alternative therapies have been explored which are designed to help in these latter stages of disease. These have included the use of deep brain stimulation in certain strategic sites within the basal ganglia network which help ameliorate not only the complications of drug therapies but also treat the underlying condition itself. However these therapies are still only symptomatic and in order to effect a curative therapy a more definitive procedure needs to be done to either rescue the dopamine cells using growth factors or replace them with neural transplantation. I will embark on a discussion of neural transplantation in the context of Parkinson's disease. This treatment has been available for a number of years and has produced conflicting results. At its best it can produce a major improvement of the symptoms which is long lasting whereas at its worst it can itself lead to severe side effects with dyskinesias that requires further neurosurgical intervention. The reasons as to why these disparate results exist and whether the current strategy using human fetal tissue in advanced Parkinson's disease is the most sensible way forward will be discussed. In particular I will explore the reasons behind these conflicting results and hope to lay out a logical argument as to issues

facing any cell therapy in Parkinson's disease, and how these can be addressed and resolved.

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Controlled release of antiretrovirals

Hagen von Briesen

Treatment of AIDS using combinations of antiretroviral drugs has highly reduced the HIV-1 related morbidity and mortality provided that the plasma viral load can be maintained as low as possible. However, eradication of the virus does not seem attainable with the present strategies of interventions, which is due to two major obstacles: if resistant mutations appear virus will escape further treatment, and latent virus reservoirs exist that cannot be reached with the current treatment regimens. One of these sanctuaries is the mononuclear phagocyte system (MPS) with its HIV-1 target cells, such as monocytes/macrophages (MO/MAC), dendritic cells (DC) and Langerhans cells, which can be considered as primary cells for viral entry and subsequently are responsible for distribution of the virus throughout the organism into various tissues. Colloidal drug carriers are easily phagocytosed by MO/MAK. Therefore, they can facilitate the uptake of antiviral drugs by these cells and may enable a considerably improved AIDS therapy. Strategies will be discussed which allow targeting of antiretroviral drugs to these cells by the use of carrier systems.

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Intravaginal rings for the long-term, controlled release of HIV microbicides

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The devastating effects of the HIV/AIDS pandemic continues unchecked in the developing world, with some 25 million people living with HIV in Sub-Saharan Africa at the end of 2004. According to UNAIDS. The most obvious solution to stopping the spread of HIV/AIDS is a safe and effective HIV vaccine, but this is far from imminent. Therefore, other preventative strategies are urgently needed. It has recently been estimated that heterosexual transmission of HIV now accounts for over 90% of adult infections worldwide and that male-to-female transmission of HIV is eight times more likely than female-to-male transmission (Lamptey 2002). A clear scientific rationale therefore exists for the development of female-controlled preventative strategies. The most promising approach is the development of effective vaginal microbicides (Malcolm et al 2004), chemical agents that have the potential to either prevent or reduce HIV transmission when applied to the vagina prior to intercourse. The availability of an effective, robust drug delivery system is an essential prerequisite for the effective implementation of a vaginal microbicide strategy in the developing world. The intravaginal ring (IVR) device is, perhaps, the best example of a specific intravaginal delivery device best suited as an HIV microbicide delivery system. The device is typically constructed from a hydrophobic elastomeric polymer,such as silicone, and offers prolonged, controlled drug delivery combined with ease of self-insertion and removal by the patient. Several IVR products for contraception and hormone replacement therapy are now commercially available (Woolfson 2002). This paper considers the controlled, prolonged release of a novel vaginal microbicide, TMC 120, a non-nucleoside reverse transcrtiptase inhibitor, from silicone IVR devices of reservoir design. TMC 120, a dianilinopyramidine derivative, has a physicochemical profile well suited to release from a hydrophobic IVR, has high potency against wild type HIV-1 in nanomolar quantities and is non-irritant intravaginally (Herrewege et al 2004). In this study, in vitro release data for TMC 120 obtained under sink conditions demonstrate that zero order (linear) release profiles are obtained over 30 days for TMC 120 from intravaginal ring systems. IVR systems with a release modifier can achieve mean daily release rates in excess of 200 μg per day. Assuming a vaginal fluid plus semen volume of 16 mL, release of 200 μg per day of TMC 120 equates to a theoretical vaginal concentration of 37 mM, ignoring possible tissue uptake, a concentration in excess of that determined as microbicidal against HIV in vitro.

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TB prevention: new vaccines for an old disease

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Globally, tuberculosis (TB) kills 2 million people a year, with one-third of the world's population currently infected with the bacillus *Mycobacterium tuberculosis* (Mtb). Though the bulk of deaths occur in developing countries, TB is an increasing global public health menace, with resistant Mtb strains becoming more frequent. The only way to eradicate TB is to find an effective vaccine. The current vaccine, BCG, only protects infants from severe TB (miliary TB and meningitis). However, BCG provides only minimal and inconsistent protection against the most common and infectious forms of TB, especially in TB-endemic areas. This applies to both reactivation of latent, previously acquired infection and new and acute infection, and likely results from the waning of BCG induced immunity. Further, with more than one-third of HIV-infected people co-infected with TB and subsequently TB being one of the leading causes of death among people affected by AIDs, the fact that BCG can also be unsafe for those infected with HIV is clearly another major concern. There are a number of issues that must be considered regarding the efficacy of the BCG vaccine in the prevention of TB infection: the BCG vaccine may lack important antigens present in virulent strains of TB; it may not elicit T-cell subsets thought to be important in the control of TB; the higher prevalence of environmental mycobacteria is thought to contribute to low vaccine efficacy in such regions, and vaccine efficacy is thought to wane over time (Bramwell & Perrie 2005). Therefore, there is a clear need for new and improved vaccines. In all the above areas, particulate delivery systems may impact upon the outcome of vaccination. Once protective epitopes are defined, they can then be encapsulated in effective delivery systems to enhance their immunogenicity, potentially reduce adverse reactions (in comparison to live vaccine) and avoid the problems associated with infection caused by the vaccine strain in immunocompromised individuals. Using the ESAT-6 sub-unit antigen from Mtb, a previously demonstrated dominant target for cell-mediated immunity in the early phase of TB (Brandt et al 2000), a range of particulate vaccine systems (including liposomes, niosomes and microspheres) have been tested for their ability to induce ESAT-6 specific antibody and T-cell responses, and protective immunity compared with that achieved with *Mycobacterium bovis* BCG. These investigations have continually indicated that including a combination of the immunostimulatory agents within these formulations results in highly potent vaccine systems. Investigations regarding the physico-chemical characteristics of the tested delivery systems and their efficacy as vaccine carriers will be reported.

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Building process knowledge and understanding using Near Infrared Microscopy

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Over the past eight years, Near-Infrared (NIR) Microscopy has evolved into a system which is now important in understanding the matrix distribution of components in solid dosage forms. With the development of this technology, the distribution and size properties of each component in a formulation can be visualised. It is no longer down to theories to understand what happens to form the product matrix during processing, as NIR microscopy offers the means to visualise and fingerprint what has occurred during manufacture of a solid dosage form. The technique is critical to developing process knowledge and understanding the factors impacting product performance, which is important in the light of current regulatory discussions. In fact results from NIR microscopy experiments will be presented which show a direct correlation between the distribution of excipients and final dosage form dissolution. Different examples will be discussed where not only has NIR microscopy been used to evaluate a real production issue, but also been used to develop fundamental understanding of how the dosage form performs in end product tests. Current instrumentation allows in-depth laboratory investigations, but the future for any technique that can predict performance is process based. Therefore data will be presented that has been collected from a production blender, and used to assess content and blend uniformity within a manufacturing operation.

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Raman microscopy and pharmaceutical science

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Raman spectroscopy is an information rich technique that offers a unique blend of chemical and physico-chemical information. Significant advances in instrumentation over the past decade have been made. In particular, solid state lasers operating through to the near infrared have largely eliminated the fluorescence problem that once plagued industrial Raman spectroscopy, while CCD detectors have increased data acquisition rates. What was once considered a relatively insensitive technique can now sample sub-picogram quantities, which equates to volumes $1\ \mu m^3$. With this level of sensitivity Raman spectroscopy has recently seen a renaissance as an investigational tool, with the advances led principally by the introduction of high resolution (both spatial and spectroscopic) Raman microscopes. In this presentation, general principles of Raman spectroscopy and Raman microscopy will be outlined. The concept of imaging and chemical mapping will then be introduced, and discussed with respect to how this is implemented in different commercial instruments (global imaging versus the reconstruction of a distribution from an array of spectra). The presentation will then proceed to discuss specific examples of how Raman microscopy is applied at different stages in the pharmaceutical industry. In the early stages of the pharmaceutical process preformulation initiates characterisation of the active pharmaceutical ingredient (API). Screening for salt selection and possible susceptibility to polymorphism are important parameters that feed into later development steps. At this stage material is scarce and Raman microscopy is evolving as a pivotal technique as it is capable providing physico-chemical information working with milligram quantities. Additionally, even though a single phase has been selected, transformations can occur as a function of downstream processing steps. Again, Raman microscopy can allow in-situ structural analysis as a function of temperature through the coupling of a hot-stage with a Raman microscope. In this way, it can be used to model the effect of processing steps during formulation. In the mid stage of the pharmaceutical life cycle, Raman spectroscopy commands an important role in formulation development. Controlled release dosage forms are evolving in complexity. This places higher demands on analytical investigation tools to understand release mechanisms and troubleshoot problems as they arise. Raman microscopy is ideal in this role as exemplified by Sporanox and unlicensed variants. The Sporanox formulation is designed around the formation of a solid solution of itraconazole with hypromellose. The formation of a solid solution is important for the enhanced bioavailability of this particular drug. The appearance of unlicensed products posed a dual threat. In addition to the obvious threat of unlicensed competition, the products showed a reduced bioavailability, even though the composition was similar. Raman imaging provided an important insight into the distribution and form of the drug. Finally, the potential of Raman microscopy in protecting IP is discussed.

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Terahertz imaging

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Terahertz pulsed imaging (TPI) (Fitzgerald et al 2005; Shen et al 2005) is a quick and versatile technique for analysing and mapping the composition and physical form of materials, including 3D imaging of tablets and other dosage forms of interest in the pharmaceutical industry. In this talk commercially available products will be described, based on TeraView's TPI technology platform, and examples given of their unique non-destructive analysis capabilities in product development, stability testing and potential for at-line and on-line QA and QC. Terahertz pulsed spectroscopy (TPS) (Taday 2004; Taday & Newnham 2004; Strachan et al 2005) will also be described with emphasis on its ability to detect polymorphs and provide data that is complementary to Raman spectroscopy. The selection rules for the two techniques differ and through TPS a new data-set is obtained to aid in the identification and potential screening of polymorphs. The technique has proven particularly useful in identifying problematic polymorphs, which cannot be easily identified by Raman or other techniques. The power and versatility of TPS stems from the fact that it is a direct probe of the low frequency vibrational modes that are difficult to access in Raman, due to their proximity to the excitation line, as well as IR and other techniques. Recent work also demonstrates that TPS can be used to assess the degree of crystallinity in many materials, as well as monitor changes to the amorphous state. Terahertz spectral interpretation and instrumentation are similar to basic infrared (IR) and therefore easy to understand and use. The sample preparation techniques are similar to those used in IR. In this talk the applications of terahertz technology in analytical and process environments will be described, with particular focus on applications in the FDA's Process Analytical Technologies (PAT) initiative.

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Phytoestrogens and the menopause

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The menopause is defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity. Menopause results in many women experiencing a decrease in the quality of life. The major symptoms associated include vasomotor symptoms, vaginal symptoms, osteoporosis, breast cancer, cardiovascular disease and cognitive problems. The most common vasomotor symptoms displayed by women include hot flushes, night sweats and palpitations. Psychological problems experienced are sleep deprivation, forgetfulness, difficulty concentrating and depression. Many women also suffer from vaginal dryness, which consequently leads to loss of libido. Many of these symptoms are all linked to the declining and erratic production of oestrogen by the ovaries. Hormone replacement therapy (HRT), is most commonly prescribed for the relief of menopausal symptoms and for protection against bone loss and ischaemic heart disease. However, reports in the media, on the long-term effects of HRT have deterred its use due to the associated risks with breast cancer, myocardial infarction and strokes. As a result, increasing numbers of women have turned to complimentary and alternative medicines for relief from their menopausal symptoms. Soy and red clover isoflavones, and flax lignans have been investigated for reduction of menopausal symptoms. Activity of these phytoestrogens is thought to be related to their structural similarity to oestradiol. Phytoestrogens are bound to oestrogen receptors and may directly affect transcription of oestrogen-regulated gene products. They may also act through their antioxidant effects, and there appears to be a positive synergy between phytoestrogens and other antioxidants. Epidemiological findings have encouraged research into the potential benefits of soy isoflavones on menopausal symptoms, and soyfoods and isoflavones have received considerable attention for their potential role in preventing and treating osteoporosis. Both red clover and flax have been investigated for activity for a similar range of symptoms. Red clover, particularly in hot flushes and osteoporosis, and flax lignans have been investigated for their effects in bone metabolism, and also on menopausal symptoms, with variable results. Most of the phytoestrogens occur in their natural state as glucosides. Bioavailability of most of them requires initial hydrolysis by intestinal (-glucosidases, and after absorption they are highly conjugated to glucuronic or sulphuric acids, leaving only a small portion of free aglycone in the blood. There is extensive further metabolism of particular phytroestrogens, particularly daidzein to equol, and flax lignans to enterodiol and enterolactone, although it is not known what the biological significance of these latter metabolites is; however, these soy metabolites are produced by gut microflora and there is large inter-individual variation in this ability, which is believed to have a marked effect on overall biological activity. The quality and variability of both food sources of soy isoflavones and supplements of individual isoflavones have been reported. Data on red clover preparations and flax lignan sources have been less well documented. Adverse effects, which are generally mild, have been reported for soy and its isoflavones, but red clover and flax have no effects reported to date.

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Black cohosh and *Agnus castus*

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Black cohosh (*Cimicifuga racemosa*) (CR) extracts have, for more than 50 years, been widely used as medicinal or over-the-counter products against climacteric complaints. In 5 double-blind placebo-controlled studies it was shown, utilising the well established Kupperman Index or the Menopause Rating Scale, that CR extracts ameliorate the most disturbing climacteric symptom (i.e. hot flushes) and improve sleep behaviour. In 2 studies, a bone-protective effect was also demonstrable, while in one large open study no effect

on the endometrium was observed. Studies concerning the effects of CR extracts in the mammary gland have not been conducted so far. It is, however, highly unlikely that such effects exist as all CR extracts tested so far do not bind to oestrogen receptors. In one study in mammary cancer patients who received an additional treatment with tamoxifen, the CR extract failed to improve climacteric symptoms. The mechanisms by which CR extracts act are largely unknown. Serotoninergic and dopaminergic compounds were identified in the extract, which may explain the beneficial effects in the hypothalamus but cannot explain the effects in the bone. Extracts of the fruit of *Agnus castus* (Ac) proved to be effective in reducing premenstrual symptoms, particularly premenstrual mastodynia. Premenstrual symptoms are often associated with latent hyperprolactinemia. Severily dopaminergic compounds were isolated out of Ac extracts; the possibility exists, therefore, that reduction of prolactin release under stressful situations may be the major mechanism by which Ac improves premenstrual symptoms. As many women with premenstrual symptoms suffer from corpus luteum insufficiency and therefore from sterility Ac extracts may also be used for the treatment of this type of sterility.

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Cranberries and urinary tract infections

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Cranberries have been used widely for several decades for the prevention and treatment of urinary tract infections (UTIs). Cranberries comprise nearly 90% water, but also contain various organic substances, such as quinic acid, malic acid and citric acid, as well as glucose and fructose. No definite mechanism of action has been established for cranberry in the prevention or treatment of UTIs. However, the main suggestion is that cranberries prevent bacteria (particularly *E. coli*) from adhering to uroepithelial cells that line the wall of the bladder. Although cranberry juice is the form of cranberries most widely used, other cranberry products include cranberry powder in hard or soft gelatin capsules and cranberry tablets. This presentation describes the findings from two Cochrane reviews (Jepson et al 2005a,b), which assessed the effectiveness of cranberries in preventing and treating such infections. An extensive systematic search was undertaken to identify all randomised or quasi randomised controlled trials of cranberry juice/products for the prevention or treatment of UTIs in susceptible populations (e.g. people who had recurrent UTIs, the elderly and people with an indwelling catheter). Two reviewers independently assessed and extracted information. Relative risks (RR) were calculated where appropriate; otherwise a narrative synthesis was undertaken. Quality was assessed using the Cochrane criteria. Ten trials met the inclusion criteria for the prevention review (five cross-over, five parallel group). The effectiveness of cranberry juice (or cranberry-lingonberry juice) versus placebo juice or water was evaluated in seven trials, and the effectiveness of cranberries tablets/capsules versus placebo was evaluated in four trials (one study evaluated both juice and tablets). In four good quality RCTs, cranberry products significantly reduced the incidence of UTIs at twelve months (RR 0.65 95% CI: 0.46–0.90) compared with placebo/control. Within these studies, cranberry products were effective at reducing the incidence of UTIs in women with recurrent UTIs, but not in elderly men and women or people requiring catheterisation. There was no significant difference in the incidence of UTIs between cranberry juice versus cranberry capsules in one study (RR 1.11 95% CI: 0.49–2.50). Six trials were not included in the meta-analyses due to methodological flaws or lack of available data. However, only one reported a significant result for the outcome of symptomatic UTIs. Side effects were common in all trials, and dropouts/withdrawals in several of the trials were high. We concluded that there is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12-month period, particularly in women with recurrent UTIs. Whether it is effective for other groups, such as people needing catheterisation and elderly men and women, is less certain. The large number of dropouts/withdrawals from some of the trials indicates that cranberry juice may not be acceptable over long periods of time. In addition it is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules). The review of cranberry juice for the treatment of UTIs identified no randomised trials. Therefore there is not good quality evidence to suggest that cranberries are effective in treating UTIs.

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Herbal medicines and women's health

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Women have unique healthcare needs, which start when they reach puberty and continue throughout life. Some involve minor disorders, which are suitable for OTC medication, including with herbal medicines; others are natural life-events which (if they are to be treated at all) require management with products such as dietary and herbal supplements that are known to be safe. These may need to be taken over a long period of time, which can also give rise to possible issues with herb-drug interactions if the patient is taking prescription medicines. In general, women are also more likely to use 'natural' medicines and tend to have a greater awareness of them. In addition, they are often responsible for the family diet – which also has an impact on women's health, as shown by epidemiological studies regarding a high phytoestrogen-containing diet. A number of 'functional foods' purporting to bridge the gap between medicines and foods are now becoming available (e.g., bread made with linseed and soya flour) and some herbal medicines can also be classified as nutraceuticals. The public rarely makes any distinction between them, and as preparations from the same plant may be found in a number of forms, all will be covered here. Although herbal practitioners will treat a much wider range of conditions, with individually prescribed herbal tinctures and extracts, this talk will concentrate on those products which have been clinically tested, those already in wider usage, and which are of particular relevance to pharmacists. Queries regarding herbs are increasingly being asked of pharmacists in all walks of the profession, and arise from patients who may already be taking them, those who want advice on which to take, and of increasing importance, those involving patients who are taking prescribed drugs concurrently. The talk will cover examples of specific herbal products, such as those used for the treatment of cystitis (cranberry juice, bearberry), premenstrual syndrome (agnus castus) dysmenorrhoea (cramp bark), pregnancy (raspberry leaf), menopausal symptoms (dong quai, sage, black cohosh) and osteoporosis (soya, red clover isoflavones). Evidence for efficacy and safety will be presented and their potential for drug interactions discussed. Associated conditions, or thought to be related to those cited above, will be briefly discussed (e.g. improvement in cognitive processes, which are thought to be impaired by the menopause) and, finally, a short account of on-going research which may lead to novel methods of treatment will be given.

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Clinical aspects of diabetes

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There are 1.8 million people in the UK known to have diabetes, around 90% of whom have type 2 diabetes. It is estimated that by 2010 this number will have reached 3 million. This increase is largely being driven by an aging population and a rising prevalence of obesity. Prevention, or at least delay, of the onset of type 2 diabetes has been shown in clinical trials. There is now a need to ensure that patients at risk of diabetes have access to programmes to reduce their risk. In addition to those with known diabetes, it is estimated that a further million have undiagnosed diabetes. There is a clear imperative to screen for diabetes in high risk groups because of the insidious nature of type 2 diabetes and the high prevalence of complications at diagnosis. Initiatives including the one organised by Diabetes UK, the British Pharmaceutical Society and Lloyds pharmacy are working towards addressing this need. Diabetes is associated with a number of chronic complications, including nephropathy, neuropathy and retinopathy as well as premature mortality. There is now good evidence that systematic care aimed at achieving good glycaemic control, blood pressure control and treatment of lipids can reduce the disease burden. As the numbers of people with diabetes have swamped secondary care, the bulk of care will need to be delivered in the community.

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Build me a pancreas

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Diabetes management technology has advanced slowly over the years. The discovery of insulin was hailed as a miracle cure and, indeed, many lives were saved. However, as people survived longer it became obvious that they were

developing terrible life-limiting complications. Research revealed that tight blood glucose control was essential in limiting complications. Although insulin therapy moved towards multiple injections and modern insulin analogues, the treatment still failed to mirror normal physiological insulin secretion. Tight blood glucose control was also associated with increased frequency of hypoglycaemia, which impacted negatively on quality of life and therapy compliance. It became clear that a more physiological method of insulin delivery was needed to limit the financial and human cost of diabetes and its complications. Pancreas and, later, islet transplants, were limited due to donor availability and the requirement for immune suppression. Insulin pumps were developed in the 1970s and were initially large and unreliable. They suffered a decline in popularity within the UK and technological advancements during the last years have largely occurred within the American and European markets. Modern insulin pumps are no larger than a phone pager. They are sophisticated, safe, reliable devices that deliver short acting insulin analogues continuously via a subcutaneous catheter. They mimic the normal pancreatic secretion pattern by delivering continuous background levels of insulin augmented by extra insulin at mealtimes. The ambition of most pump manufacturers is to incorporate continuous glucose sensing into an implantable or externally worn pump that would act as a closed loop system, essentially an artificial pancreas. Unfortunately, traditional glucose-oxidase based glucose sensing systems are unreliable and unsuitable for implantation. New methods need to be developed and several efforts are ongoing to find novel in-vivo glucose sensing technologies. The race to build a pancreas is well underway and may well succeed before other biological technologies, such as islet encapsulation and stem cell manipulation, become available.

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The pharmacist's role in the delivery of diabetes care and the National Service Framework (NSF)

I. Gummerson

Historically, the mechanism for extending the role of the pharmacist in diabetes care has not been in place. Over the last few years, certain 'drivers for change' have led to more opportunities for such role extension. These have included the PSNC New Contract (NC) for community pharmacists, government documents (e.g. 'NHS Pharmacy Plan', 'Choosing Health through Pharmacy', NSF for diabetes), guidelines/ resources (e.g. RPSGB, PSNC, NPA), supplementary/independent prescribing, nGMS contract, 'pioneer' pharmacists and employers prepared to facilitate a change in practice. The NSF for Diabetes for England (www.dh.gov.uk) was launched as the 'Standards' and 'Delivery' documents. The other UK nations have similar (but not identical) documents: Scotland at www.show.scot.nhs.uk; Wales at www.wales.nhs.uk; N.I. at www.cresti.org.uk. The RPSGB guidance on diabetes care and the PSNC New Contract address many of the Standards in the NSF for diabetes. The RPSGB guidance divides pharmacist activities ethically into to 'Essential' or 'Desirable' practice. The PSNC New Contract divides activities into 'essential', 'advanced' or 'enhanced' services, reflecting specifications for funding. Linking the NSF Standards for Diabetes to potential pharmacy activities:

Standard 1 — *Prevention of Type 2 diabetes* covers raising awareness; promotion of healthy lifestyles with posters/leaflets (RPSGB 'Essential' practice; NC 'essential' service); diabetes prevention programmes (RPSGB 'Desirable' practice); 'healthy living service' (NC 'enhanced' service).
Standard 2 — *Early Identification* covers monitoring OTC sales (RPSGB 'Essential' practice); screening (NC 'enhanced' service).
Standard 3 — *Empowerment* covers education (RPSGB 'Desirable' practice).
Standards 4/5/6 — *Clinical care of adults/children* is covered in the New Contract with Medicine Use Reviews (MURs) (NC 'advanced service'); medicines reviews in care homes; full clinical medication reviews; disease specific medicine management services (NC 'enhanced services').
Standard 7 *Management of diabetes emergencies*.
Standard 8 *Care during admission to hospital*.
Standard 9 *Pregnancy* — reinforcing advice given at clinic eg not smoking, folic acid, etc.
Standards 10/11 & 12 — *Detection/management of long-term complications* (NC 'enhanced' service) covers reducing the risk of progression of complications, by encouraging good diabetes management, concordance with lifestyle advice and medication, and attending clinic appointments.
Other models of care include targeting ethnic communities for screening, disease management; diabetes/hypertension clinics in secondary care.

Even though emphasis here has mainly been on the role of the community pharmacist, the NSF standards also apply to pharmacists working in GP practices or in secondary care. In conclusion, the pharmacists' role in diabetes care is growing with the increase in opportunities brought about by an assortment of drivers for change, one of which is the NSF for diabetes. How prepared pharmacists are in general, to take up these new challenges, has yet to be seen. Factors such as; the pharmacist having a special interest in diabetes, having the time, sourcing appropriate funding and having the support of his/her employer may all play a part. It will be interesting to look back in 5 or 10 years, to see just how far pharmacists have progressed.

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Alginate in cell therapy and tissue engineering applications

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Alginate is a polysaccharide extracted from seaweed and kelp. Alginate is used in many food applications where it imparts a thickening effect (salad dressings) or contributes to gellation (restructured foods, bakery fillings). But where and how do alginates impact on human health? Alginate fibres have been used for decades in many wound-healing bandages. Here alginate absorbs fluid from the wound and provides a moist, oxygen permeable, barrier. Alginate is also used in oral tablets as a binder or disintegrant, and is a major component in heartburn (acid-reflux) preparations such as Gaviscon. However, with the availability of ultra-purified and well-characterized alginate, more demanding applications for this biopolymer are being developed. In the areas of tissue engineering and drug delivery there is a need for structural materials that possess specific functionality. Alginate has shown interesting potential for use as a scaffold material in tissue-engineered medical products, in drug delivery formulations, and as an encapsulating matrix for the immobilization of living cells. Alginates are now being used in bone regeneration, nerve regeneration, and tissue bulking applications. Another application utilizing the gelling properties of alginate is the immobilization or encapsulation of living cells to form artificial organs and cell therapy constructs. Here, cells in an alginate solution can be entrapped inside an alginate gel bead by dripping into a bath of calcium chloride where gelling occurs instantaneously. The porosity of the alginate bead is such that oxygen and nutrients can enter the gel while cell products such as proteins – up to certain molecular weights – can diffuse out of the gel. The gel is, however, not porous to antibodies and immune cells such as macrophages. This alginate gel 'biofactory' can then be implanted into an animal or man and act as a continuous production system for, for example, insulin. The efficacy of alginate-encapsulated cells that produce tumour inhibiting substances is now being evaluated for the treatment of brain cancer in dogs in a 5$^{th/}$ Framework EU supported project together with the Animal Health Trust, Newmarket, UK. Specific cellular interactions can be induced by the biopolymer conjugated with cell growth or attachment factors. In one example vascular endothelial growth factor (VEGF) is incorporated into an implantable biopolymer matrix. While no blood vessel grow around the implant without VEGF, they do when VEGF is incorporated into the matrix. Alginate can be modified with specific receptor binding substances such as the RGD peptide sequence. The RGD sequence is common to many extracellular matrix molecules. RGD-alginate can then be used to assist in tissue formation. By using RGD-alginate, it has been shown that chondrocytes form much more cartilage when immobilized than in alginate without the RGD sequence. For all applications utilizing alginate, knowledge of the composition and sequence of the biopolymer will determine many functional aspects. Therefore, characterization of the alginate used gives important information that can affect its successful use in medical applications. The need for a hydrated environment, controlled degradability (or not) and non-irritating (i.e. biocompatible) materials has directed interest to the natural biopolymers, such as alginate, chitosan and hyaluronate. Improvements in the quality, characterization and repeatability of such biopolymers have led to reconsidering them as components of tissue engineering (TE) and cell therapy products. Some of the unique properties that these biopolymers can bring to the TE field are: instantaneous or controlled gelling at physiological conditions; bioadhesiveness as in the case of chitosan; lubricity as in the case of hyaluronate; and specific cellular interactions that can be induced by the biopolymer alone or conjugated with cell growth or attachment factors. Alginate gel beads implanted into rat brain have shown moderate loss in cell viability but extended endostatin release for periods of up to 6 months. Visualization of the anti-angiogenic effect on C6 rat glioma growth, tumour vasculature and microhaemodynamics have been demonstrated by using intravital video microscopy. The technique showed that endostatin greatly affected tumour-associated microcirculation but did not appear to affect normal microcirculation. The local delivery of endostatin seems to specifically affect tumour-associated microvessels by reducing the vessel density (sprouting) diameter and functionality. Tumour cell migration and invasion was greatly reduced in the endostatin-treated animals. Work is in progress to determine the therapeutic

dose of endostatin delivered by the encapsulated cell system. The pre-clinical efficacy of this new therapeutic technology will be evaluated in dogs presenting primary brain tumours. These dogs will be treated following tumour resection by implanting encapsulated endostatin producer cells within the resection pocket. BioStructures manufactured from ultrapure biopolymers have use as scaffolds in tissue engineered products, as drug-containing gels, pastes or solids for depot delivery, and as an encapsulating matrix for immobilization of living cells. BioStructures are now being used for bone regeneration, nerve regeneration, tissue bulking, and as components of artificial organs. Of critical importance to the success of such TE applications is the commercial availability of these biopolymers as purified, well-characterized and regulatory approvable products. Improvements in the quality, characterization and repeatability of such biopolymers have led to reconsidering them as components of TE and cell therapy products. Biopolymers manufactured in accordance with cGMP guidelines are now available, some also in a sterile form.

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Designing an inhaler: from concept to industrialisation

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Inhalers can be categorised into metered dose inhalers (MDIs), dry powder inhalers (DPIs), nebulisers and atomisers. To illustrate the principles of inhaler design, the focus of this presentation will be multi-dose dry powder inhalers, which are becoming more predominant. Designing an inhaler is rather like undertaking a long journey, which may be easy or problematic and unexpected events are always possible. Detailed planning of activities and resources, together with risk mitigation strategies, are thus highly desirable and add valuable structure and thought into the design route. Before beginning the journey, it is important to consider the needs of all stakeholders both within (manufacturing, marketing, regulatory etc.) and outside (patient, health care professionals and regulatory agencies) the organisation overseeing device development. Stakeholder needs are captured in the Product Design Specification (PDS), which must thus be unambiguous in content and well understood by all who will use it. The next step is to brainstorm a range of device concepts that can then be evaluated against the PDS to select a few lead concepts. Key principles of device operation can be practically evaluated through production of rudimentary test rigs. Hopefully, a candidate design emerges, which can be formally defined, preferably using a CAD workstation. The inhaler may now be visualised by using the computer's 'solid modelling' capability and rapid prototypes made by processes such as stereolithography. Confirmation that the inhaler design meets all expectations, may include limited pharmaceutical performance testing, further market research, patent infringement analysis and a detailed design review. Stakeholder feedback is included in future design iterations. Selection of a device manufacturing company and filling/assembly equipment manufacturers can also commence. Additionally, an external design consultancy can provide impartial design input and also challenge the design (e.g. Failure Mode and Effects Analysis). A 'soft' design freeze enables single cavity injection mould tooling to be produced, which will provide devices suitable for definitive performance and robustness testing and Phase I/IIa clinical trials. The outcome of the testing programme will likely highlight areas for further design improvement and following instigation of these changes and subsequent retesting, the design can ideally be frozen. Ahead of pivotal clinical studies (late Phase IIb/Phase III), there must be no further changes to the drug product that could affect performance. Additionally, Ph III clinical supplies must be manufactured at the commercial launch site using manufacturing equipment and processes that are representative of the eventual commercial process. To ensure Ph III studies can progress in a timely manner, early consideration must be given to selection of commercial site, scale-up/technology transfer strategy etc. Congratulations, your part of the design journey is complete.

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Parameters that influence the performance of DPI formulations and their interactions

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Studies on adhesive mixtures for inhalation in the past ten years have proved that the fine particle fraction from a DPI depends on many variables. It is well recognised that drug and more particularly the carrier surface properties are two major determinants for the interactive forces in these mixtures. Carrier surface properties have (for instance) been expressed in terms of rugosity, the presence of adhering fines, surface impurities, water of adsorption and amorphous spots, and the relevance of these variables has been investigated under quite different circumstances, using different carrier payloads, different mixing conditions and different inhaler devices. A complicating factor for drug-to-carrier interaction studies is the occurrence of inertial and frictional forces during the mixing process, which could either act as press-on forces, increasing the adhesive forces between drug and carrier, or as kneading forces resulting in drug agglomeration on the carrier surface. The degree of agglomeration is not only relevant to the adhesive forces in the mixture but also to the detachment forces during inhalation. The magnitude of these inertial forces during mixing depends on the bulk properties of the carrier fraction used and the intensity of the mixing process, but their effect can be reduced, or even be eliminated, by sheltering the drug particles in carrier surface discontinuities from these forces. Whether sheltering is effective depends on the carrier payload in relation to the size and volume of the carrier surface discontinuities. And finally, whether this sheltering improves the fine particle fraction from a DPI or not, depends on the type of detachment forces generated during inhalation. Considering the great number of variables and the recognition that certain variables interact with each other, it may not be surprising that the outcomes of DPI-performance studies are not all of the same tenor. Many examples of conflicting conclusions can be given. It should therefore be recommmended to focus future investigations rather on the interactions between the variables than on the influence of single paramaters. From the investigations so far, it can be concluded that at least five different aspects should all be taken into consideration in such future investigations when using currently marketed (unmodified) lactose products as drug carrier in inhalation powders and when comparing the results from such studies with each other: firstly, the binding capacity and degree of saturation of the so-called 'active carrier sites' regarding drug particle adhesion with high interparticulate forces; secondly, the storage capacity of large carrier surface discontinuities providing drug particles shelter from press-on forces during mixing (as well as from certain types of detachment forces during inhalation); thirdly, the magnitude and effectiveness of inertial and frictional (press-on forces) during mixing; fourthly, the intensity and duration of the mixing process; and finally, the type and magnitude of the detachment forces generated during inhalation.

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Triggering polymer architectures to deliver

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Current trends in polymer science directed towards the development of polymer therapeutics and biomedical engineering highlight the importance of structural precision, hierarchical ordering and scope for fine tuning the functions of interest in those materials. The ability of polymer chemists to control structural complexity of polymeric materials has significantly increased over the last 5–10 years and continues on this path. Dendrimers, for example, are being actively pursued for drug delivery, making use of their high surface functional group density for cell targeting and as a means of enhancing drug potency through multivalency effects. Supramolecular architectures, exemplified by polyrotaxane, offer new mechanisms for drug delivery as it has been shown to control, locally, the delivery of high drug concentrations within short time intervals through the use of specific chemical triggers. In this presentation we will discuss the synthesis of new polymer architectures, how these architecture are combined with specifically chosen chemical triggers and what effect the combination of polymer structure and in-built stimuli-responsive behaviour has on the envisaged therapeutic function of these materials in the context of gene and drug delivery.

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Temperature-responsive polymers in pharmaceutical science: from microarrays to controlled release

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Temperature-responsive polymers have attracted considerable interest in pharmaceutical science due to their ability to change their conformation in response to an external stimulus. In this seminar we will show that poly(N-isopropylacrylamide) (PNP) polymers have potential to fulfil different pharmaceutical applications, from microarrays to controlled release when appropriately designed. When PNP is grafted to surfaces the responsive surface is able to capture dispersed model protein particles when triggered by a temperature

increase. This has potential application in microarray preparation. PNP co-polymers can also be used to design oil-in-water emulsions that gel when heated. These emulsion gels can release oil-soluble solutes and the technology has potential application in controlled release, which is discussed. PNP can also be constructed as microgels. These are responsive colloidal polymer particles that are crosslinked and swell with water at room temperature. The PNP microgel particles show the ability to take up solutes from water when heated. It will be shown that ultrasound can be used to remotely trigger uptake for these systems.

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E-medicine: connecting in to the network

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The human brain and nervous system operate electro-chemically. Almost all traditional medicine is chemical in nature. Recently, however, through the use of implanted electrodes, so electronic medicine has started to be seen, not only as an alternative, but a technique with much more to offer. Different implant methods will be considered here and their use for such as Parkinson's Disease treatment and stroke rehabilitation will be presented. Social and ethical aspects of the methodology will be balanced with the immediate therapeutic treatments available as opposed to the possibilities of both mental and physical enhancements for man. Through a series of self-experimental trials, various clinical applications for implant technology are being investigated. Practical human recipient results thus far will be presented, these to include the direct employment of neural signals for the control of networked technology and vehicle movement. Also presented will be the use of neural signals for the control of wearable computing and the apparent new world opened up by directly linking the human nervous system with the Internet. This latter concept is exciting from the point of view of bodily extension mechanism, in that neural signals can control devices remote to the individual, but realises potential problems due to signal interchange ability, causing software viruses to re-emerge as their biological equivalents. In particular, a study involving the use of a microelectrode array, implanted through neurosurgery, will be presented and described in terms of its mode of operation and the response of the human recipient's body. Body acceptance/rejection, possibilities of infection and stabilization of the implant will all be considered. With the array in place, neural signals associated with muscle contraction were transmitted to a computer either via a hard wire link or through a radio transmitter unit. By this means, a range of devices were controlled. The recipient was also allowed to learn to perceive feedback information to fully operate a prosthetic hand and a mobile platform. In the experiments carried out thus far, as well as therapeutic possibilities, a number of enhancement trials were carried out. Of these, two are particularly pertinent. Firstly, ultrasonic sensory output was fed directly onto the nervous system to give the recipient a new, sonar, sense relating directly to distances of objects from the recipient. Secondly the recipient was also able to take part in the first radio telegraphic communication test between the nervous systems of two humans — the basis for thought communication. Finally, some possibilities for the future, with established brain-computer interfaces will be described. These will include not only thought communication and the electronic treatment of a range of medical problems, but also the opportunity to electronically modify memory.

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Emerging strategies for treatment / management of colorectal cancer

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Until the latter part of the 1990s 5-fluorouracil (5FU) was the only recognised active cytotoxic in the treatment of colorectal cancer. Treatment options were therefore limited with modest benefits observed in the use of 5FU in the adjuvant and palliative setting. Most research was directed at how best to administer this single active agent (i.e. bolus or infusion); biochemical or immunological modulators. The new millennium has seen significant developments in the treatment of colorectal cancer with the introduction of four novel agents (oxaliplatin, irinotecan, bevacizumab and cetuximab) and several oral fluoropyrimidine formulations. This rapid increase in the number of active agents for colorectal cancer has thrown up many questions as to the timing, sequence, combination, benefits and toxicity of treatment at all stages of the management of this disease. In addition cost effectiveness and overall treatment costs are beginning to raise questions about how, and if, such treatments can be used, even in well funded healthcare systems. The first arena in which novel agents were tested in colorectal cancer was advanced disease. Large randomised trials have shown that addition of oxaliplatin or irinotecan to standard 5FU based regimens results in improved outcomes in chemonaive or 5FU resistant disease. Such regimens have become standard first line treatment in many countries. However, evidence suggests that the exact sequence or combination may be less important than exposure to all of these active agents at some point in the course of therapy. The development of agents targeted against critical determinants of the cancer cells' malignant phenotype has, over the last few years, begun to show clinical benefit. Drugs acting to inhibit growth signals or their receptors (e.g. cetuximab) and those acting to prevent the development of the new blood vessels required for tumour growth and metastasis (e.g. bevacizumab) have resulted in improved response and survival when compared with standard comparators. Despite these improvements, advanced colorectal cancer remains an active research area for novel therapies. The benefits of this progress in advanced disease are now being studied in the adjuvant setting. Neo-adjuvant combination chemotherapy and improvements in surgical technique have resulted in more patients undergoing resection of liver or lung metastases with proven survival benefits. Combination chemotherapy has recently been shown to significantly reduce the likelihood of relapse compared with adjuvant 5FU alone but at the risk of greater toxicity and cost. Standard 5FU regimens are often not user-friendly, requiring multiple hospital visits or indwelling venous catheters with their inherent problems. Novel oral fluoropyrimidine preparations have been shown to have equal efficacy and less toxicity compared with intravenous 5FU in adjuvant and palliative treatment. Although being preferred by patients and now being tested in combination with other active agents, a system in which the patient is a participant in the administration of their chemotherapy raises new safety and service issues.

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Is isolated intestinal human tissue a useful tool for drug absorption assessment?

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Drug permeation across isolated fresh human intestinal tissue mounted in a vertical Ussing chamber can used to evaluate drug absorption potential in vivo. The technique has the advantage of using morphologically intact, biochemically active human intestinal tissue to perform investigations intestinal permeability. Permeation of compounds can be tested across different intestinal regions to assess site-specific absorption in the intestine. The apparent permeability coefficient (Papp) of passively or actively transported compounds is ranked based on comparison with a moderately permeable reference compound, atenolol (50% absorbed in vivo), and a highly permeable reference compound, antipyrine (98% absorbed in vivo). Our experiments demonstrate that the Papp values of a large set of structurally and pharmacologically diverse, passively absorbed compounds are well correlated with the fraction absorbed in vivo in man. In addition to testing the intrinsic capability of compounds to permeate across human intestinal mucosa, the effect of formulation excipients on that permeation can also be investigated. Our experiments have demonstrated that different excipients, used in oral formulations, effect paracellular and active transport pathways in this tissue. These results indicate that investigation of formulated compounds in isolated human tissue may reveal useful information to direct further steps in drug development.

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Significance of intestinal drug efflux transporters for oral absorption

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P-glycoprotein (Pgp) and other related efflux transporters are highly expressed by the epithelial cells that line the gut, where they have a primary role in tissue defence by pumping toxic xenobiotics back into the gut lumen. However, most attention has focussed on their ability to transport a diverse range of orally administered drugs, and in doing so, potentially influence their permeability and overall bioavailability. Transporters may modulate oral drug pharmacokinetics in several ways. Pgp can both directly limit absorption and increase elimination across the gut wall in to the lumen. In addition, inhibition or induction of intestinal Pgp also appear to be significant mechanisms underlying drug-drug interactions that lead to elevated or reduced absorption, respectively. Despite this, the quantitative significance of Pgp for human intestinal absorption, particularly compared with other sites such as the blood-brain barrier continues to be a subject of considerable debate and uncertainty. While in vitro screening (e.g. in Caco-2) suggests that a high proportion of drugs and new chemical entities interact with Pgp, many of these exhibit good oral bioavailability.

Nevertheless, the potential for significant transporter effects remain and there is a need to develop better predictive models for gut transporters, in terms of confirming or indeed ruling out adverse effects. Part of the problem lies in our relatively poor understanding of the multiple factors that may influence Pgp activity in the gut, including regional variations in Pgp expression and function, transporter kinetics, the impact of passive permeability and the contribution of non-Pgp transporters. There is also a need to evaluate the predictive value of cell-based assays with more in vitro:in vivo correlations of transporter function including the use of ex-vivo tissue models. This presentation will discuss progress in these areas using examples from published and unpublished data.

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Application and experience in the EU of BCS in the review of new generics

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After the launching of the scientific concept of the BCS (Amidon et al 1995), this was incorporated in the regulation of the USA (FDA 2000). Incorporation in the EU regulation followed one year later (EMEA 2001). The FDA and the EU regulation with respect to biowaivers are nearly fully harmonized. Both the FDA and the EU biowaiver regulations are applicable to new generic applications and to variations to existing drug products. Up to now, the FDA received very few applications for new generic products. In the EU, some marketing authorizations based on BCS were granted. The data submitted for the first successful BCS-based application in Germany, for sotalol HCl, were published (Alt et al 2004). However, also in the EU only a few applications for new generics were made. The reason for the very limited use of BCS for applications for new generics is not clear. It could be that few new generics are developed that fall into the present BCS criteria (i.e. IR solid oral dosage forms, containing BCS Class I Active Pharmaceutical Ingredients (APIs)). It might also be that the conservative additional requirements for biowaiving (i.e. high solubility of the dosage form and similarity of the dissolution profiles of the dosage form and the comparator) are too strict. However, the main reason seems to be more fundamental. A "biowaived" new generic has never been administered to man. Both the pharmaceutical industry and the regulators seem to be uncomfortable with that idea. Indeed, parameters such as the ability to swallow the medicine, taste, appearance, etc., are not detected by in vitro testing as per BCS. This point needs to be resolved. In the meantime, a general extension of biowaiving to BCS Class II and BCS Class III seems a bridge too far (Yu et al 2002). However, widening of the boundaries of BCS Class I to APIs with a fraction dose absorbed from > 90% to > 85% is considered now by the WHO, as well as opening biowaiving of BCS Class II and III, based on a risk assessment of that particular API. In this context, risks will be defined not only as the probability of reaching an incorrect biowaiver (i.e. declaring a drug product to be bioequivalent onin vitrodata, whereas the drug product would fail an in vivo bioequivalence study), but also with respect to the ramifications of this decision in terms of public health and risks to individual patients.

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The HOMER trial: an RCT of medication review in older people. A detailed description of the intervention, and an analysis of whether results differed by pharmacist characteristics

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Drug treatment in the elderly is often complicated by multiple medications, age-related physiological changes and adherence difficulties. These complications may increase hospitalisation and mortality, and decrease quality of life. Medication review in the elderly is now being widely implemented. We wished to investigate whether home-based medication review by pharmacists could decrease hospital re-admission in the elderly and improve quality of life when compared with standard care. This trial, as previously reported, demonstrated that the medication review intervention increased hospital admissions by 30% ($P = 0.009$) (Holland et al 2005). This unexpected finding has provoked interest in the intervention undertaken. This presentation describes in more detail the pharmacists' interventions, and investigates whether the results differed according to specific pharmacist characteristics.

The HOMER trial recruited 872 participants (437 intervention and 435 control) aged over 80 during an emergency admission (any cause) if returning to own home/warden-controlled accommodation, and taking two or more medicines daily. The intervention involved two pharmacist home visits within two and eight weeks of discharge. Pharmacists educated patients/carers about their drugs, removed out-of-date drugs, informed GPs of drug reactions/interactions and informed the local pharmacist if an adherence aid was needed. An analysis was undertaken as to whether admission rates differed within the intervention group according to the type of pharmacist who performed their medication review. Pharmacists were grouped according to the following categories: period since first registration (above versus below median); numbers of interventions performed (above versus below median); higher degree obtained versus no higher degree; previous experience of medication review versus no previous experience; and hospital pharmacist versus other. Twenty-two pharmacists participated in the study. The majority (68%) were experienced community pharmacists (mean age 42 years), 76% had some form of postgraduate qualification. First visits lasted a mean of 62 min and second visits a mean of 42 min. Review pharmacists noted adverse drug reactions (ADRs) or drug interactions in 33% of visited patients. Pharmacists reduced inappropriate drug storage from 7% to 2% of visited patients by their second visit ($P = 0.04$) and reduced hoarding of unnecessary drugs from 40% of visited patients to 19% ($P < 0.001$). First visits generated a mean of 1.8 recommendations/comments and second visits a mean of 0.94 recommendations/comments to GPs: 70% referred to medication issues or monitoring. 62% of recommendations/comments required some form of action: 35% were acted on, 20% were not and in 44% no data were available. Analysis of admission rates by pharmacist characteristics did not identify any characteristic associated with a significantly different rate of admission. The HOMER intervention's process findings suggest that the intervention was conducted in a similar way to interventions in many other medication review studies. The intervention was as long, or longer, than other home visit interventions. The review pharmacists identified a similar prevalence of ADRs to those identified by other studies (Krska et al 2001: Sellors et al 2003). Comparison of the proportion of recommendations enacted between this study and other medication review studies reveals that, while HOMER findings were in line with studies involving multiple pharmacists (Sellors et al 2003), far fewer recommendations were enacted than in those studies involving single pharmacists (Zermansky et al 2001), or those where there was close liaison between the reviewers and the physicians involved (Krska et al 2001). Finally, the increased rate of admission observed in the intervention group of this trial appears not to have been related simply to the experience or type of pharmacists involved.

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From process understanding to control by PAT in tablet manufacturing

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An important part of the PAT initiative from FDA is the improved process understanding that can be achieved by proper selection and adequate use of PAT tools. The development of new advanced process sensors in combination with new modelling/simulation techniques related to particle processing technology will enable process optimisation and control. Indeed, robust tablet formulations have been developed during the last 10-20 years thanks to an increased knowledge of physicochemical properties of particles and granules, a result of basic scientific research on granule formation and compaction. Still, scale-up and transfer of manufacturing methods for different unit operations from R&D to a manufacturing site or between manufacturing sites are not trivial. For example, for new processing equipment with geometric layout and different operating conditions, the manufacturing process will evolve in a different manner compared with the old equipment. The presentation will discuss how different PAT tools can be used in an integrated way from laboratory scale to full manufacturing scale to build quality into new products. Selected applications of how different PAT tools can be utilized for advanced process control, real-time quality control and process characterisation/validation will be presented.