Invited Abstracts

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Lymphatic drug delivery: opportunities and challenges

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The lymphatic system shadows the vasculature throughout the body, but is rarely acknowledged as an important conduit by which drug molecules may be transported and distributed in-vivo. The specialised structure and function of the lymphatics provides opportunities for the drug delivery scientist to both target the delivery of drugs to the lymph and lymphoid tissue, and to enhance 'conventional' delivery to the systemic circulation. From the standpoint of conventional oral delivery, drug transport by the intestinal lymphatics circumvents the first passage through the liver and may therefore enhance the bioavailability of drugs that exhibit high first-pass metabolism. Lymphatic transport may also alter systemic drug disposition and clearance patterns which are central to the interpretation of both efficacy and toxicity profiles. From the perspective of directed or targeted delivery, the lymph and lymphoid tissues are rich in lymphocytes, act as a repository for bacterial and viral pathogens and also serve as the primary conduit for the dissemination of metastases from a number of solid tumours. As a result, drug delivery strategies that enhance lymphatic transport may improve the utility of various immunomodulators, vaccines and anti-invectives and also provide a delivery benefit for cytotoxic agents designed to combat the spread of metastases from solid tumours.

These presentations will briefly overview the factors affecting drug access to the lymphatics, and examine the potential benefits of lymphotropic delivery strategies. Lymphatic access via two separate mechanisms will then be discussed. Firstly, the transport of lipophilic drugs via the intestinal lymph after oral administration and the factors that affect this process will be examined, and data presented to show that considerable lymphatic drug transport could be achieved after oral administration of appropriate lipidic formulations to fasted subjects. Secondly, the role of the lymphatics in the absorption and disposition of therapeutic proteins after subcutaneous administration will be highlighted and the emerging relationship between molecular weight and the extent of lymphatic transport described. Recent data suggesting that absorption of proteins with molecular weights in excess of approximately 35 kDa occurs exclusively via the lymphatics will be described.

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Psychopharmacological effects of *Bacopa moniera* (Brahmi)

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Natural products have been employed for their therapeutic effect in the management of neuropsychiatric disorders such as psychosis, depression and anxiety. *Bacopa moniera* (BM) also referred to as *Bacopa monieri* or *Herpestris moniera* is a medicinal plant used for centuries in the Ayurvedic system of medicine. BM known as Brahmi in Sanskrit is a perennial creeping plant found throughout India in wet, damp and marshy areas and is used in the treatment of epilepsy, hysteria and insanity in Ayurveda. BM has gained popularity in Western countries as a 'brain tonic' capable of improving mental ability and memory. BM contains many saponins of which bacosides A and B are found to be important active principles. Anxiolytic, tranquilizing, smooth muscle relaxing, bronchodilatory, cognition-enhancing, anti-oxidant, anti-cancer, immuno-modulating and anti-inflammatory effects of BM are revealed in pharmacological studies. Anxiolytic activity is comparable to benzodiazepines without affecting motor deficit. The advantage of BM over benzodiazepines is in the fact that it promotes cognition unlike the amnestic action of the later. It attenuates the retrograde amnesia produced by stress, ECS, and scopolamine. Memory-promoting effect in animal models of Alzheimer's disease is reported from various studies. It did not provide complete protection against chemo-convulsion. When combined with phenytoin, it showed higher degree of anticonvulsant activity against maximal electroshock induced seizure. BM possesses significant anticholinesterase activity, which may account for its memory enhancing action.

Its antioxidant effect has been revealed by its inhibitory action of lipid peroxidation, which is lesser than Vitamin E. Extract has cytotoxic effect on Sarcoma-180 cells in-vitro. It has anti-inflammatory effects in large oral doses in various experimental models of inflammation. In addition, it enhances proteinkinase activity and produces increase in protein in hippocampus. Clinical trials have confirmed the improvements in memory and in epilepsy. BM has been well tolerated by humans without any adverse effects. Chemical intervention with subsequent advanced studies may throw light on the therapeutic applications.

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Delivering therapeutic cells and proteins to enhance tissue regeneration

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A pharmacist in 1953 could not have predicted the remarkable drugs discovered over the 50 years to the present day. As scientists have unravelled the relationships between the genome and proteome, identified receptor-mediated signalling pathways and classified stem cells, new targets for therapy have arisen. This deeper understanding of cellular and molecular biology has generated new therapeutics based on proteins and cells. Therapeutic cells and proteins have the advantage of being able to interact with target sites in the body in complex and sophisticated ways. For example, bone morphogenetic protein-2 can trigger a signalling cascade that promotes new bone formation or young nerve cells can restore damaged connections in adult brain.

The pace of development of new therapeutics that promote tissue regeneration is fast. It has been widely predicted that new therapies for bone, cartilage, skin, liver, kidney and spinal cord will become available in the not-too-distant future. However, such "regenerative medicine" products pose difficult challenges to regulators, clinicans and industry. Central to these challenges is the complexity and fragility of therapeutic protein and cells. It is well known that many proteins are denatured by minor disturbances to their environment. This problem is intensified when therapeutic cells are developed because cell phenotype must be actively maintained.

Pharmacy has an important role to play in translating regeneration medicine ideas into successful treatments. The successful manufacture, storage, transport and clinical application of therapeutic proteins and cells are extensions of the Pharmacists role in industry and hospital. This talk will focus on the science of drug delivery as applied to regenerative medicine. New methods of drug and cell delivery are required to optimise the regenerative capabilities of these therapeutics. In particular, the location, timing of release and nature of 3D environment must be controlled by the delivery mechanism.

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Epigenetic approaches to overcoming drug resistance

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Although cancer was originally viewed as genetic disease, increasing evidence in recent years has demonstrated an equally important role for epigenetic phenomenon, including alterations in DNA methylation and changes in histone modifications. Of particular importance is the increased DNA methylation of CpG islands, a feature of essentially all tumour types. CpG islands are frequently found at the 5' end of genes and hypermethylation of these CpG islands leads to transcriptional repression of the associated gene. In addition to genes involved in tumour development, genes known to influence chemotherapeutic drug resistance

or sensitivity are also frequently targeted by this mechanism. Re-expression of such methylated genes can lead to suppression of tumour growth or sensitisation to chemotherapy. This raises the possibility of therapeutic intervention as a number of drugs are already known that can inhibit the enzymes responsible for methylation of DNA. 2'Deoxy-5azacytidine (decitabine) has been widely used in tissue culture to re-activate genes silenced by hypermethylation of their CpG islands. Decitabine treatment of cisplatin resistant cancer cell lines, both in-vitro and in-vivo as mouse xenografts, leads to re-expression of genes known to be involved in drug resistance and re-sensitisation to a number of important chemotherapeutic drugs. Based on these and other results the potential utility of decitabine as a modulator of chemosensitivity is currently being tested in clinical trials. Inhibitors of another key epigenetic change, histone deacetylation, are also being widely investigated as potential chemotherapeutics, both as single agents and also in combination with DNA methylation inhibitors. The combination of these two classes of drugs has been shown to enhance re-activation of hypermethylated tumour suppressor genes, as well as allowing gene re-activation at lower drug doses, reducing the possibility of dose limiting toxicities. Finally, DNA methylation may also serve as an important predictor of chemotherapeutic response. Micro-array based analysis of CpG island methylation in ovarian tumour samples identified a link between high levels of CpG island methylation and disease free survival suggesting that DNA methylation status may be a useful marker for predicting response to chemotherapy.

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Can plant extracts help treat alcohol dependence?

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Alcohol dependency is a major world health concern. In the past two decades alcohol related research has progressed significantly. However, the development of suitable medications for the treatment of alcohol dependency remains a challenging goal. Medical plants have been used for the treatment of alcohol dependency in eastern cultures for centuries, but these plants have only recently attracted the attention of western medicine. Several plant extracts have been shown to be effective in reducing excessive drinking in genetic animal models of human alcoholism.

Extracts of the common plant *Hypericum perforatum* L. (St John's Wort, SJW) have been successfully used for the treatment of mild to moderate depression since ancient times. Recently, it has been shown that the extract of SJW can significantly reduce alcohol intake in different strains of alcohol preferring rats. Although the mechanism of action of the extracts of SJW on alcohol intake is not fully understood, the ability of the extracts to affect serotonergic, dopaminergic and opioidergic systems in mesolimbic regions in the CNS, directly or indirectly, might underlie the efficacy of the extracts in the treatment of mild to moderate depression and alcoholism.

Recently, it also has been demonstrated that isoflavonoids isolated from the kudzu (*Pueraria lobata*) plant are effective in reducing alcohol intake. Daidzin, a major active principle of an ancient Chinese herbal treatment (*Radix puerariae*, RP) for alcohol addiction, has been shown to suppress alcohol intake in Syrian golden hamsters, alcohol preferring rats and African green monkeys. Inhibition of the oxidative pathways of monoamine metabolism has been proposed as its mechanism of action. It also has been demonstrated that puerarin, the most concentrated isoflavonoid in kudzu, reduces alcohol intake in several strains of alcohol preferring rats. Antagonism of benzodiazepine and/or 5-HT2c receptors have been suggested in the action of puerarin.

Ibogaine, one of the principle indole alkaloids found in the root bark of the African shrub *Tabernanthe iboga* (Apocynaceae family), and one of its nontoxic analogue (18-methoxycoronaridine, 18-MC) has been shown to reduce alcohol intake in several strains of alcohol preferring rats. Dopaminergic, serotonergic, endorphinergic and glutamergic systems have been implicated in the mechanism of these compounds.

Overall, although the true mechanisms of action of these compounds on alcohol intake are not fully understood, it is proposed that these compounds exert their effects by modulating serotonergic, dopaminergic, GABAergic, and opioidergic systems, which have been implicated in drinking behaviour. The role of these compounds in the future of pharmacotherapy for alcoholism depends upon the outcome of carefully conducted clinical trials.

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The complexities of drug absorption

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Significant recent work has focused on predicting drug absorption from drug structure. Several misperceptions regarding the nature of absorption seem to be common. Among these is that intestinal absorption, permeability, fraction absorbed and, in some cases, even bioavailability, are equivalent properties and can be used interchangeably. A second common misperception is that absorption, permeability, etc., are discrete, fundamental properties of the molecule and can be predicted solely from some structural representation of the drug. In reality, drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors, physiological variables including regional permeability differences, pH, lumenal and mucosal enzymology, and intestinal motility, among others. This presentation will explore the influence of these different variables on drug absorption and the implications with regards to attempting to develop predictive drug absorption algorithms.

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Prediction models for oral absorption

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One of the challenges facing the pharmaceutical industry is to improve its efficiency in selecting and developing potential drug candidates. Understanding the factors that govern drug behaviour are crucial to making rational decisions regarding both the chemical design of drug compounds as well as formulating to compensate for less than ideal characteristics. To this end, the objectives of the presentation are to describe a mechanistically based model that simulates the processes of drug dissolution, absorption and pharmacokinetics, and to demonstrate how the model can assist in drug selection and development.

Because poor aqueous solubility is one of the most common problems encountered by both medicinal and formulation scientists, accurate modeling of dissolution under non-sink conditions is critical in deciding when solubility will limit absorption, whether milling will help, and gauging the magnitude of the formulation effort needed to solve the solubility problem when no alternate drug candidates are available. For dissolution, the Noyes-Whitney equation will be presented followed by discussions as to how the equation can be used to simulate the dissolution of polydisperse drug powders under non-sink conditions. Model generated simulations will be compared with actual dissolution data to validate the dissolution part of the model. Coupling of the dissolution model with a compartmental pharmacokinetic model provides a broader perspective of issues facing drug candidates. Also presented will be the maximum absorbable dose (MAD) calculation that provides an easy way to determine an approximate upper limit to absorption based on solubility and the absorption rate constant.

Other modeling innovations to be discussed include treating the solubility, absorption rate constant, and dissolution volume as continuously changing time-dependent properties. This treatment allows for simulation of drug precipitation, changing permeability along the length of the gastrointestinal tract, and water absorption or secretion from the intestinal lumen and its affect on dissolution and drug absorption. This approach will be compared with modeling the

gastrointestinal tract as a series of distinct compartments, each with its own constant parameters. Simulations comparing constant versus time-dependent parameters will also be shown.
Finally, a discussion on expanding the model to simulate controlled release will be given. A retrospective analysis applied to nifedipine will be used to show how the model could have guided the development of that drug.

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Successful formulation approach to overcome low solubility and variability

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Numerous potent lipophilic drugs exhibit low oral bioavailability due to their extremely poor solubility in aqueous media. For this class of compounds, defined by Amidon et al (1995) as 'low solubility/high permeability class compounds', dissolution in the gastrointestinal tract is the rate-limiting step in the absorption process.
Microemulsion preconcentrates are clear mixtures of a lipophilic component, a hydrophilic component and a surfactant, with optionally containing a hydrophilic co-component and/or co-surfactants. Upon dilution with aqueous media, oil in water microemulsion droplets of usually less than 200 nm (150 nm) are formed spontaneously. Thus, microemulsions provide the lipophilic drug in a highly dispersed system. After dilution with water, the main characteristics of microemulsions are their isotropicity, optical transparence, and thermodynamical stability.
Microemulsion preconcentrates can be administered as drink solution, and soft- or hard-gelatin capsules. Upon contact with gastric and intestinal fluids, the fast formation of small microemulsion droplets ensures an optimal use of the absorption surface and leads to a significant improvement of rate and extent of absorption of lipophilic drugs while lowering the variability of pharmacokinetic parameters. Microemulsion formulations are relatively unaffected by the physiological state of the gastrointestinal tract, such as pH, food interaction, bile, etc.
The presentation will cover formulation approaches for the development of microemulsion preconcentrates for the oral absorption improvement of lipophilic drugs and discuss their main physicochemical and biopharmaceutical aspects.

Amidon, G. L., Lennernas, H., Shah, V. P., *et al.* (1995) *Pharm. Res*. **12**: 413–420

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NIR methods of detecting counterfeit products

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At the Centre for Pharmaceutical Analysis, London School of Pharmacy, we are collaborating with the Medicines and Healthcare products Regulatory Agency (MHRA) and Pfizer to investigate the capabilities of Near Infrared (NIR) spectroscopy and NIR microscopy for the identification of counterfeit medicines. These counterfeit medicines may be seized by the MHRA or other regulatory agencies abroad. Suspect products are then either submitted to the manufacturer for confirmation of authenticity or to the Medicines Testing Laboratory for testing. Existing techniques are time-consuming, require skilled personnel and are based on separative techniques such as GC and HPLC, looking for residual solvents, or testing for the presence of the active ingredient and determining its quantity.
Initial studies to-date using NIR reflectance spectroscopy have shown that tablets originating from different sites of manufacture can be distinguished from each other (helpful in identifying tablets that have been 'diverted') and that counterfeit Viagra can be distinguished from the authentic product. NIR spectra representative of the authentic product are stored in a library database to which unknown samples could be compared using chemometric methods of analysis such as Correlation in Wavelength Space and/or Principal Component Analysis. Benefits of the technique include its rapid scan time and the fact that it does not require sample preparation or skilled personnel to acquire the data. It is hoped to develop a method for a portable NIR instrument that would allow rapid detection of counterfeit tablets in-situ.
The relatively new technique of NIR microscopy has been used to obtain spectral images of tablets and blends for the purpose of process control. Small areas, typically 30 microns square, are scanned to produce a single NIR spectrum and an image map is created. Often counterfeit products are sophisticated, containing the active ingredient in similar amounts to the authentic medicines, which means that simply testing for the presence or absence of the active is insufficient. The use of NIR microscopy would allow for not only the identification of individual components in a product, but also determination of their relative distribution and percentage composition, all of which can be compared to the properties of the authentic product. It is likely that NIR techniques of analysis will play a useful role in supplementing existing techniques used to identify and verify counterfeit products.

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Application of population approaches to paediatric drug dosage regimen design

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Lack of information about drug handling in neonates and children has often led to drug dosage regimens being determined empirically rather than from research studies. However, undertaking research in a paediatric population has inherent ethical and practical difficulties. For example, "conventional" pharmacokinetic studies involving individual analysis of full drug concentration–time profiles are not easy to perform due to restrictions on the number of blood samples that can be withdrawn, especially from neonates and infants. In recent years, however, the "population approach", which allows the simultaneous analysis of "sparse" data from a large number of subjects, has increasingly been applied within clinical practice and drug development. Many of these studies have focussed on paediatric patients, where the opportunity to utilise sparse data has particular advantages.
There is widespread use of antibiotics with narrow therapeutic ranges, such as gentamicin and vancomycin, in premature neonates. Serum concentrations of these drugs are measured in the course of routine clinical care and are used to guide dosage alterations for individual patients. However, although these drugs have been available for many years, "optimal" concentration-time profiles were only identified relatively recently and, consequently, some "traditional" dosage regimens have proved to be inappropriate. In an audit of gentamicin use, Lannigan & Thomson (2001) found that only 3 out of 22 published sets of neonatal dosing guidelines would have achieved target profiles in more than 50% of patients. Similar problems were encountered with vancomycin, where only 33% of patients given "standard" dosage regimens achieved target trough concentrations (Grimsley & Thomson 1999). A study was then conducted in which vancomycin dosage histories and concentration data were analysed using the population pharmacokinetic package, NONMEM (Beal & Sheiner 1992). This analysis found that vancomycin clearance was strongly influenced by weight and serum creatinine concentration and led to the production of new dosage guidelines based on these clinical factors (Grimsley & Thomson 1999). Initial evaluation of the new guidelines indicated an improvement in practice with 72% of measured trough concentrations within the target range. However, application of the guidelines within another hospital was less successful and resulted in a further study that compared three sets of vancomycin population parameter estimates, each with different explanatory clinical variables (Thomson & Sie 2003). A modified set of guidelines has since been produced and is currently being evaluated.
Population methodology offers the opportunity to utilise pharmacokinetic data generated during routine clinical care and conduct research when conventional approaches are not feasible or ethical. This methodology is therefore of particular value in designing drug dosage regimens for paediatric patients.

Beal, S. L., Sheiner, L. B. (1992) *NONMEM User Guides, parts 1-VII*. Technical Report. University of California, San Francisco
Grimsley, C., Thomson, A. H. (1999) *Arch. Dis. Child. Fetal Neonatal Ed.* **81**: F221–F227
Lannigan, R., Thomson, A. H. (2001) *Paediatr. Perinat. Drug Ther.* **4**: 92–100
Thomson, A. H., Sie, A. (2003) *Paediatr. Perinat. Drug Ther.* **5**: 116–123

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Taste masking for paediatric formulations using stearic acid microspheres

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Taste masking remains a persistent difficulty in the preparation of medicines for children, the challenge being to prepare dosage forms that will mask the taste of the drug yet will also release the active in a satisfactory manner after ingestion. This presentation will outline work that has taken place in collaboration with GlaxoSmithKline on the use of stearic acid microspheres as a means of masking the taste of an antibiotic, cefuroxime axetil, with work performed by Dr Hazel Robson, Dr Simon Gaisford and Ms Sheng Qi. In brief, the drug and stearic acid are prepared as microspheres by a spray chilled process whereby a molten mix of the two components are sprayed through an atomising nozzle into a cold air stream, resulting in solidification of the binary system into spheres that may then be incorporated into suspension formulations. However the mechanism by which taste masking and subsequent release takes place is still a matter of investigation. The presentation will outline initial studies in which it became clear that the stearic acid was reacting with the dissolution medium, through to later investigations whereby we have investigated the nature of the structure formed on exposure to alkaline media and the physical chemistry of the interaction, with a view to understanding the fundamental behaviour of these systems. In this manner it is hoped that formulation using this promising approach can be optimised for a range of further drug substances for paediatric use.

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Predicting poor permeability and formulation approaches to overcome it

Bruce Aungst

Absorption Systems

Intestinal membrane permeability is one of the major factors influencing oral bioavailability, together with solubility and pre-systemic metabolism. Medicinal chemistry efforts to enhance pharmacologic activity often result in increased molecular weight or H-bonding groups, and consequently can result in poor membrane permeability. Major drug discovery programs now commonly include screens for intestinal permeability before a compound is dosed orally. Once correlations are established between the measured or calculated property and in vivo human absorption, these screens enable ranking the compounds within a series with regard to oral absorption potential. Then the more time-consuming in vivo studies are performed on compounds with the best chance for success. Correlating permeability results with structural or physical chemical properties can also be a useful guide in driving chemistry toward creating permeable and active new compounds. The types of permeability assays employed range from computational predictions based on structure only, artificial membrane permeability measurements, and cell culture (Caco-2) membrane permeability measurements, to excised intestinal tissue permeability studies from rat to man. The usefulness and shortcomings of the most typical permeability models will be discussed, with examples of their application. Sometimes there are compounds that have high apparent therapeutic value, but which also have low oral bioavailability because of poor intestinal permeability. This could include permeability problems due to efflux transport mediated by P-gp or another transporter. In these cases a strategy to improve bioavailability using permeability-enhancing excipients might be adopted. Here also it is important to understand the usefulness and limitations of the assays used to assess permeability enhancement, because some of these may not be predictive of the in vivo effects of the enhancing agent. This lecture will attempt to briefly review the status of the area of formulation research to enhance intestinal permeation. Formulation and excipients intended to increase passive diffusion permeability have not yet reached the product stage, although various approaches are in clinical trials. The limitations of this approach will also be discussed. Excipients that modulate the function of efflux transporters could also be used to increase intestinal absorption, and several of known inhibitors are currently available off-the-shelf.

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Quality systems suitable for small-scale manufacture

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The requirements of GMP do not differentiate between large and small-scale manufacturers, the same standards apply to both. Therefore, any quality system in a small-scale operation has to deal with the same issues, and achieve the same outcomes, as that of the largest multinational. This may seem rather a gloomy conclusion, given the title of this talk, but there are options open to allow a small manufacturer to operate a quality system to meet the requirements of GMP.

Firstly, the design and operation of such parts of the quality system as documentation can be quite simple; paper documentation is adequate where a larger company might need electronic document systems to cope with the multiplicity of sites and processes. While electronic systems certainly bring many advantages, the computer system validation and electronic signature security requirements would completely abolish benefits for the smaller manufacturer.

Secondly, small-scale manufacturing operations can sometimes be designed to reduce the "GMP overhead" incurred. A good example is manufacture of APIs. On a large scale, this requires fixed plant, which requires considerable qualification, and most particularly, unless it is dedicated to a single product, cleaning validation and verification. For small-scale synthetic operations, the reactions can be carried out in glass vessels, which can be dedicated to a single product, and when the project is complete the glassware can be discarded. Cleaning then becomes much simpler, and the burden of cleaning validation and verification, beyond a simple visual examination, is removed.

Thirdly, the small-scale manufacturer can reduce the amount of effort that he needs to put into operating this quality system by judicious use of contractors and consultants, the contracting out of work that does not justify setting up in-house capability, and bringing in expertise as and when needed, but only for the period that it is needed.

Contractor selection should include both technical evaluation and an evaluation of the contractor's quality system. It is important that this evaluation is carried out, as ultimate responsibility for product quality lies with the contract-giver, no matter how sophisticated the contract-acceptor's systems. Therefore, for a small manufacturer, it is probably best to select established contractors with robust quality systems of their own.

Similarly, consultants can be used for a range of tasks that do not justify full-time employees in a small-scale operation, or where a task may require a lot of effort, but only for a short time. Examples are facility and equipment qualification, supplier and contractor auditing, batch certification by a QP, and staff training.

In all cases where work is contracted out, to a contract analytical or manufacturing facility, or to a consultant, it is vital that there is a contract in place that details the scope of the work, which party is responsible for what, and the standards required. By using some or all of these options, a small-scale manufacturer can operate a quality system that meets the full requirements of GMP.

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Strategic aspects of drug delivery: the role of academia and the drug delivery network

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Drug delivery research has been defined as "the multidisciplinary research that underpins the development of a drug from a compound designed to interact with a specific pharmacological target into a medicine that is practical and convenient to use and (most importantly) displays the desired clinical benefit (Royal Pharmaceutical Society of Great Britain Working Party on Drug Delivery 2001). A drug varies from being a small relatively stable molecule to a macromolecule; the British biotechnology industry is responsible for over half of the 300 drugs currently under development within the European Union (Coughlan 2003). A working party established by the Royal Pharmaceutical Society of Great Britain produced a report that identified the highly fragmented and uncoordinated approach to drug delivery research within the UK.

The UK has a number of internationally recognised academic drug delivery research groups who receive funding from research councils, charities and industry. Research council funding is usually restricted to priority areas, which can exclude activities that fit within the definition of drug delivery. Industry is a major partner/sponsor of academic research (directly or via schemes such as TCS, Link, and CASE studentships). The establishment of such links can often arise almost by chance, and a lack of co-ordination in 'bringing together' expertise can exclude many potential contributors, including small to medium enterprises (SMEs). The research assessment exercise (RAE) has also focussed academic researchers towards publication and income generation. Innovative research is favoured by Research Councils while 'nearer market' research is preferred by many commercial sponsors, leaving a potential 'development' gap in the middle.

One of the RPSGB working party's key recommendations was therefore to establish a 'drug delivery network' to "co-ordinate the strategic development of UK Drug Delivery Research and thus maximise its effectiveness" and to be a "virtual centre of excellence with the participation of academic and industrial groups". The establishment of such a network was supported during discussions at two subsequent research council sponsored Drug Delivery workshops.

A proposal for funding such a network has now been submitted to the EPSRC. It is proposed to run initial workshops specifically as a means of bringing a multidisciplinary group of academic researchers, SMEs and larger companies together to explore innovation opportunities and current drug delivery challenges. Key drug delivery priorities will be identified from which more focussed 'ideas and innovations' workshops will be organised, leading on to the formation of 'clusters' for bids for funding (including 'Link' and 'Faraday' schemes). A network website will be developed providing information on current funding opportunities, a database of stakeholder groups and any consortia requiring specific expertise. This will be supplemented with articles and information in pharmaceutical publications. The network will work in partnership with other national and international networks and groupings, research councils and regional development agencies, and act as a lobbying community that can advise agencies and help inform policy decisions.

It is intended that the network will become self-financing and therefore continue beyond the three-year funding period. The network represents a bold attempt to co-ordinate and encourage innovation in this important area of research. Success will be judged ultimately by its ability to promote the development of research activity that enhances the international competitiveness of the UK drug delivery research community.

Coughlan, A. (2003) *New Scientist* **178**: 54

"UK Drug Delivery Research: The way forward in the New Millennium". Report on the Royal Pharmaceutical Society of Great Britain Working Party on Drug Delivery. February 2001

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Biopharmaceutical issues associated with the parenteral route of administration

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The success of biopharmaceuticals and the challenges faced by drug discovery programmes which are leading to the production of candidate drugs with less than ideal oral delivery properties underline the need for the re-evaluation of the oral route as the expected route of drug delivery. These factors, an increasing understanding of the added clinical value of parenteral depot therapy and technology advances made, indicate that parenteral delivery should be viewed as a clinically exciting and commercially important route for the chronic delivery of drugs.

Successful and rapid development of new parenteral therapies for chronic delivery requires a meaningful understanding of the biopharmaceutical attributes of the intra-muscular and sub-cutaneous routes so that the candidate drug and delivery system can be designed to provide maximum synergy and performance. There are many processes that can be rate limiting in the absorption of drugs after intramuscular or subcutaneous injection. These include dissolution of the drug, release of drug from a drug delivery matrix, partitioning of drug from an oily vehicle, diffusion and or perfusion of the drug molecule through the tissue, diffusion or perfusion of the vehicle from the injection site, perfusion of fluid to the injection site and removal of drug from the absorption site by blood or lymph. The impact of these processes of drug absorption will be highlighted.

Polymeric (PLGA) based systems will be discussed. Generally for drugs encapsulated in PLGA delivery systems all processes will be rapid relative to drug release from the delivery system. It will be demonstrated that preclinical animal and human physiology pertinent to 'preformed' PLGA formulation performance is similar. Thus preclinical models may be used to predict the clinical performance of PLGA based delivery systems. The importance of understanding how changes in administration impact on the physiology/formulation interaction and subsequent interpretation of data will be emphasised.

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Advanced aseptic processing and packaging by Blow-Fill-Seal technology

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Blow-Fill-Seal technology is a well-established pharmaceutical process; ideal for filling of liquid or semi-solid aseptically produced products. The process is recognized as an advanced form of aseptic processing according to USP, but can also produce terminally sterilized products. The packaging materials used include, but are not restricted to, polyolefinic materials such as poly(ethylene) and copolymers of poly(propylene).

The presentation will give a general description of the process and explain some various machine types available and possibilities in package design. Advantages and disadvantages of the technology will be highlighted and the mechanisms of microbial and endotoxin contamination will be discussed. Some examples from development of parenteral products in Blow-Fill-Seal presentations will be brought up, and finally, US and EU guidelines related to this exciting processing technology will be discussed.

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Innovations in pulmonary delivery and their implications for patient care

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The last decade has seen the development of many new pulmonary drug delivery technologies. These developments have been driven by three factors; the need for CFC replacements for pressurized metered dose inhalers, the need for highly efficient and reproducible delivery for macromolecules and the realization that improvements in compliance could be a major contributor to better therapy in diseases such as asthma and COPD. As a result of these technological advances the percentage of the nominal dose that can be delivered to lung has risen to as high as 80% and coefficients of variation of the dose delivered to lung has fallen to as low as 15%. These technologies have been, and are being, applied to both small and large molecules.

The potential benefits are numerous. For example macromolecule delivery via the lung can replace injections and should lead to greater patient compliance and convenience. Insulin is an example that is in clinical development. Other macromolecules and peptides have similar potential. Also for small peptides and small molecules the speed of absorption from the lung may improve the speed of onset of pain and migraine medications. In asthma spacers and breath-actuated devices are becoming common and these should lead to more reliable delivery and possibly improved efficacy.

Overall the last decade, although driven by some very specific needs, has opened-up pulmonary delivery to new applications which should bring many benefits to patient population.

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Compassionate supplies 'an overview'

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For patients suffering with a life-threatening condition where either current licensed drugs are ineffective, or where there is no marketed product available, supplies undergoing research and development may be provided via a compassionate release programme.

Compassionate supplies are unlicensed medicines that may be made available where a special clinical need exists. They may be provided under emergency use protocols or on a named patient basis.

The provision of compassionate supplies is subject to varied legislation and regulatory controls across the globe. However, evidence suggests that policies tend to facilitate or encourage the use of compassionate drugs.

When considering compassionate supply, it is critical to evaluate the pros and cons for the sponsor, the treating physician and the patient. The sponsor has opportunity to collect additional safety data, and may accumulate data in populations excluded from formal clinical trials; yet the sponsor must also consider the ethics of such supply, validity of data collected, treating physician freedom and resources for running a programme. For the physician and patient there is new hope for recovery, pre-approval experience and free drug; equally there are risks and ethical considerations. A big question is whether it is ethical to save a life with a research medicine, where safety and efficacy may not be fully known, where dose-ranging studies may be incomplete, and formulations commercially unviable? This moral dilemma may suggest a deeper issue: do those that have access to the medication have an obligation to provide the drug and are there limits to ethical duties? (Answers to these questions fall outside the scope of this presentation but nevertheless need to be considered.)

For the sponsor, management of compassionate supplies may consume a vast amount of resource, from Clinical Project Managers, Clinical Research Associates/Organisations, Pharmacy and Supply Chain Logistics through data management, regulatory and safety groups. Invariably, some compassionate requests fall outside the usual 9–5 working week, and so provision of an out-of-hours service will need to be established where patient eligibility is assessed, a drugs order raised, supplies dispensed, despatched and distributed expediently.

An assessment of patient eligibility should exist; there should be a screening program where inclusion/exclusion criteria are established. Patients undergoing this assessment are often not eligible for formal clinical trials (e.g. paediatric population).

Responsibilities must be clear and unambiguous; the treating physician is responsible for obtaining country specific regulatory approval and local approvals, s/he performs initial screening, obtains patient consent and collects safety and efficacy data; the sponsor must provide information about the drug (e.g. safety and efficacy information, dosing instructions, reconstitution/delivery instructions). Both parties have a duty to assess the risk/benefit ratio. There is 'risk' of administering a medicine where safety and efficacy are not fully known, and there are legal and ethical issues. Conversely there is 'benefit' of successful treatment of patients, in-use experience of the drug and the collection of new data.

In conclusion, compassionate supply is complex, there are ethical considerations and resource issues; it requires an appreciation of multifaceted legislative and regulatory requirements whilst seeking to preserve yet protect life.

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Making the best of available drug treatment

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As the number of new drugs coming on to the market declines, and costs of their development escalates, we must become more adept at getting the most from existing drugs. In this presentation I will focus on two areas which impact on the effective use of existing drugs. These areas are very different and distinctive, namely, the problems with patient adherence with prescribed regimens and secondly the issue of the use of off-label drugs in paediatric patients.

It has been often said that methods of prediction of poor adherence with medication regimens are no better than flipping a coin. Early research has often borne this out, however, more recent data would suggest that there are certain underlying conditions and patient beliefs, which can lead to non-adherence. The better known of these are the number of doses required per day, the side-effects of drugs involved and whether the condition being treated is asymptomatic. The recent focus has, however, been on psychosocial parameters (e.g. beliefs about medicines, beliefs about disease, self-efficacy and locus of control). Also there is increasing evidence that depressed mood has a negative impact on adherence as has the involvement of the patient in the decision making process of drug selection. These issues will be explored in relation to making the best use of available medicines.

In relation to drug use in children, up to 50% of medication in general paediatric wards and up to 90% of drug use in intensive care units, is in an unlicensed or off-label manner. This puts children at an obvious disadvantage in relation to drug safety and efficacy as drug dosage often has to be guestimated. Although there are excellence published texts to help prescribers, these are often based on experience rather than on properly conducted dose ranging studies. There is therefore a need for much greater research efforts in this area. Population pharmacokinetics offers one very useful approach to remedy this lack of evidence and it is this area that will be explored in the presentation, again with a focus on getting the most benefit from existing drugs.

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Targeting the pancreatic islet beta cell in Type 2 diabetes mellitus — prospects for novel treatments

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Controlled studies have shown that optimal control of blood glucose can prevent the microvascular complications of type 2 diabetes mellitus and there is some

evidence that this may also be true for macrovascular complications. However, optimal glucose control is not often achieved. Type 2 diabetes is characterized by defects in insulin secretion and insulin action (Gerich 1998). Thus the pancreatic beta cell remains an important target for drugs and several clinically important agents (sulphonylureas, such as glibenclamide, glipizide and gliclazide and meglitinide analogues such as repaglinide and nateglinide) work through augmenting insulin secretion.

Glucose-induced insulin release occurs in response to meals and prevents post-meal hyperglycaemia. The effect of glucose is amplified by a number of mechanisms, including the incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon like peptide 1 (GLP-1), which are secreted from the gastro-intestinal tract and which work primarily by activating adenylyl cyclase in the beta cell, leading to increased formation of the cyclic nucleotide cyclic 3'5'AMP (Creutzfeldt 2001). There is considerable interest in exploiting the action of incretin hormones, especially GLP-1, and their analogues in the treatment of type 2 diabetes. Another, or complementary approach, may be to inhibit the destruction of beta cell cyclic 3'5'AMP (cAMP), which is rapidly destroyed by phosphodiesterase (PDE) enzymes, this being the only known mechanism for inactivating cyclic nucleotides. Currently there are 11 known gene families of CN-PDEs consisting of more than 50 enzymes with differences in their substrate selectivities (cyclic AMP vs cyclic GMP), kinetics, allosteric regulation, tissue distribution and susceptibility to pharmacological inhibition. Several PDE enzymes have been identified in the pancreatic islet, including the calcium-calmodulin activated PDE1, the cyclic GMP-inhibited PDE3 and the cAMP-specific PDE4. There is considerable evidence that PDE3 is the important isoenzyme regulating the cAMP pool relevant to insulin secretion, although there is also evidence to support a role for PDE1 (Pyne & Furman 2003). This talk will discuss the possibilities and limitations of exploiting mechanisms leading to increased formation, or reduced destruction, of beta-cell cAMP in the treatment of Type 2 diabetes.

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