PHARMACEUTICAL PHYSICIAN

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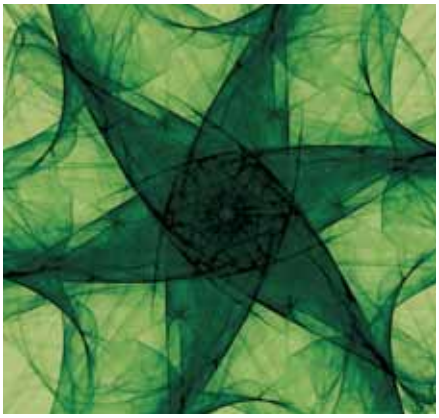
BrAPP Education Day 2015

PPhinal PPHunnybone



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STOCK MARKETS OPENED the year with record falls around the world. But the pundits predict a good year for us in pharma/biotech with research and development productivity continuing at pace. Has there ever been a better time to work in our industry?

Starting at the end of the journal- Hugh Gibbons draws his series of PPhunnybones to a close marking his 50 years in our industry. He has witnessed change a-plenty and has thrived on it developing one of the most interesting careers I have come across yet. Over the 23 years during which our paths have crossed, Hugh has demonstrated a hunger for development-both his own and for others, contributing to the career trajectory of many tyro pharmaceutical physicians – an appetite for challenge and, above all, cheerful and intelligent resilience. None of these attributes goes out of fashion and all remain essential to the success of a PP today. I am sure you will join me in thanking Hugh for PPhunnybone and wishing him health and happiness.

Bob Ings and Colin Vose, who many of you know from the BrAPP/ University of Cardiff Postgraduate Course in Pharmaceutical Medicine, draw their series on pharmacokinetics to a close with a useful article summarising the practical applications of a pharmacokinetic approach in drug development today. The series has been very well received by this journal's readership and I am delighted that Bob and Colin have been prepared to put in so much time and effort to share their enthusiasm and understanding of the topic more widely. Those of you taking the Dip Pharm Med exam may usefully choose to incorporate the series into your revision… For the rest of us, a welcome reminder of things we thought we knew. Thank you, Bob and Colin.

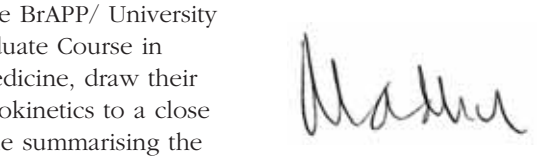
I also need to thank the MHRA for two items. The first is a timely piece on career development reminding readers of the diversity and value of the roles available at the regulatory agency. The other showcases a recent Early Access to Medicines Scheme and illustrates, perhaps, how it could be utilised to the advantage of all stakeholders by your company?

The recent BrAPP Annual Education Day was a great success. Liz Langley has drafted a summary of the day for those of you who were unable to attend including a precis of the inaugural Anne Appleton lecture, given in memory of Anne, a relatively young PP and enthusiastic BrAPP committee member, who passed away last year.

Last but not least, Dr David Glover has enjoyed a stellar career in pharma and his memoire is reviewed in this issue. As the reviewer notes "David argues that he may have enjoyed the heyday of the blossoming industry but for those us who remain and those of you to come it behoves us to keep the banner flying. This book may help you reflect on ways to do that."

And on that positive note, I will end.

Here's to a great 2016.



Dr Madhu Davies

Dr Madhu Davies

SPECIAL FEATURE:
Pharmacokinetics – an overview
Applications of Pharmacokinetics

By Drs R. M. J. Ings and C. W. Vose


Bob Ings


Colin Vose

1. INTRODUCTION

THIS IS THE last of six articles aiming to provide an overview and understanding of the principles, processes and applications of pharmacokinetics (PK) in Pharma R and D. This article summarises the specific PK studies applied and the value of resulting information. Some of these applications have been mentioned in other articles of the series and these and some additional sources of information are listed in the bibliography[1,2,3,4,5,6,7].

Factors affecting the efficacy and safety of a drug can be identified, understood, and managed if its PK is well-characterised and the relationship between the PK and the pharmacodynamics (PD) is understood. With this knowledge, the PK characteristics of a drug can be used in:

- Drug discovery and selection
- Species differences and their implications such as validating the choice of species for toxicology
- Dosage regimen design
- Assessment and implications of non-linear kinetics
- Predicting possible drug-drug interactions
- For an orally administered drug, understanding the role of first pass metabolism as well as the effect of food on absorption.
- Understanding the effect of physiological factors such as age, weight, gender etc.
- Understanding the effects of disease, both that being treated and other unrelated diseases such as renal and hepatic failure, and its therapeutic implications

2. DRUG DISCOVERY SUPPORT

Historically, drug leads and development candidates were selected predominantly on their preclinical efficacy, potency, selectivity and toxicity. However, given high failure rates in clinical development, associated, in part, with poor PK properties *(Figure 1)*[8], PK properties are now assessed early in discovery programmes. The application of *in vitro* and *in vivo* PK in discovery was recently reviewed by McGinnity et al[9].

The overall objective is to select a development candidate most likely to show required *in vivo* PK properties and desired PD in man.

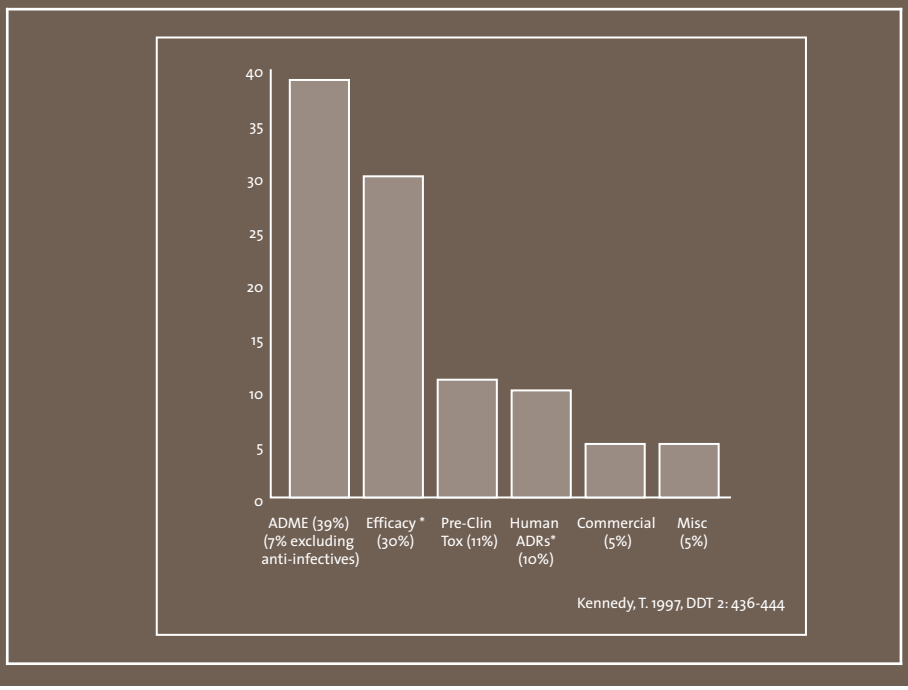
2.1 In vitro screening

The process of understanding potential PK properties of a drug can start even before the compound is first synthesized.Two broad fundamentals will influence the PK of a drug:

- The physico-chemical properties of the compound
- The physiology of the subject receiving the compound

Drug design cannot do much about the latter but the former is very much in the hands of the medicinal chemist. Many physico-chemical properties e.g. molecular weight, Log P, Log D, pK_a, polar surface area (P.S.A), number of

| FIGURE 1: Reasons for failure of drug candidates in development
(Redrawn based on information from T. Kennedy, Drug Discov. Today, 2, 435-444, 1997)



| TABLE 1: Physico-Chemical Properties of Drugs and Pharmacokinetics

PROPERTY	INFLUENCES
Structure	Molecular weight (Size) Partition/distribution coefficient (Ratio of solubility in lipids and water) Chemical stability pKa (acid/base/non-ionic)
Partition Coefficient (logP) Distribution Coefficient (logD)	Solubility in biological fluids, Absorption Protein binding Distribution Elimination pathways (excretion vs metabolism)
pKa (Acid/Base/Non-ionic)	Absorption Distribution Elimination
Molecular Weight	Membrane transport Biliary excretion

hydrogen bond donors and acceptors can be calculated in silico from the proposed chemical structure, even before its synthesis. This is important since the relationship between chemical structure, physico-chemical properties and PK is the basis of chemical modification(s) to optimize PK properties. The influence of the relevant physico-chemical properties on PK are summarized in *Table 1*.

Once compounds have been synthesized, their physico-chemical properties can be further evaluated by a series of relatively high throughput exploratory *in vitro* screens. Initially these properties include solubility, permeability (PAMPA), metabolic stability using microsomes, plasma protein binding and cytochrome P450 (CYP-450) inhibition. These screens weed out those compounds having little

chance of success in further development. Based on the properties of the early drug leads, new analogues with modified structures and physico-chemical properties will be prepared. The aim is to find compounds with a clearance, volume of distribution, and half-life, that together with appropriate absorption and bioavailability will, using a simple dosage regimen, provide steady-state plasma levels (C_{ss}) with low to moderate within- and between-subject variability, yielding the required PD.

However, at this stage of the process the tendency can be to view each of these screens as a filter with sharp cut-off criteria, optimizing one property and then moving to the next. This approach can be protracted and costly and invariably leads to very few or no potential development candidates, especially as optimizing one property can easily compromise another. It is far better, periodically, to assemble all the data and evaluate it in a multidimensional manner using programs such as Spotfire (TIBCO, CA) to visualize the overall profile and determine if it is worth further evaluation.

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As the compound moves from hit to lead and lead optimization, more detailed, lower throughput *in vitro* assays can be introduced, including dissolution, Caco-2 cell monolayer assessment of permeability and any P-gp efflux transporter involvement, more detailed plasma protein binding the CYP-450 Ki (inhibition constant), and time- and mechanism-based inhibition and transporter inhibition.

Metabolite profiling comparisons in liver microsomes/cells of the pharmacological and toxicology species and man will support interpretation of pharmacology activity and toxicity. In addition, reaction phenotyping can identify the human enzymes and/or transporters eliminating the drug, whilst, binding to the PXR and CAR nuclear receptors and functional hepatocyte assays of specific CYP-450 isozymes can assess enzyme induction potential. Covalent binding studies and glutathione adduct formation can be evaluated looking for reactive metabolites. If appropriate, these more detailed assays can be performed with the regulatory submission in mind. Also, intrinsic clearance (Cl_{int}) calculations (equation 1) can be made to predict the human clearance (equation 2) as described by Houston[10] to avoid high first pass metabolism of orally administered compounds.

When concentrations are <Km *In vitro* $Cl_{int} = \frac{V_{max}}{K_m}$ ... ...(1)

Where V_{max} = Maximum metabolic rate; K_m = Michaelis constant

In vivo $Cl = \frac{F_u * Cl_{int} * Q_h}{F_u * Cl_{int} + Q_h}$ ... ...(2)

Where F_u = Fraction unbound in plasma; Cl_{int} = intrinsic clearance; Q_h = Liver (hepatic) blood flow

More sophisticated and robust human predictions can be made by bringing much of these data together using physiologically-based pharmacokinetic models, looking for possible drug-drug interactions and the PK in special patient populations by employing programs such as SimCyp (Certara, CA) or GastroPlus (Simulations Plus, CA).

2.2 In vivo Preclinical

The *in vitro* assays described above indicate the potential PK of a compound which must be tested in a variety of *in vivo* animal models since the early safety assessment will be performed in a rodent (usually rat) and non-rodent species (usually dog or monkey). Initially single dose PK studies are performed to evaluate exposure in the species of interest and combined with some formulation development if exposure is inadequate e.g. poor oral absorption due to poor dissolution.

These studies are followed by repeated dose PK studies, commonly performed in conjunction with toxicokinetic studies used to ensure adequate exposure to the drug and/or specific metabolite(s) in the toxicology studies. The single dose PK data from the different species can be used to predict the likely PK in man (Cl, V_D and $t_{1/2}$), prior to dosing to man, using allometric scaling. This relies on the relationship between parameters of various physiological processes[11] e.g. liver blood flow, creatinine clearance (a measure of kidney function), heart rate, respiratory rate, maximum lifespan potential, and bodyweight (BW) in animal species as described in equation 3. Since many of these processes affect the elimination of foreign compounds e.g. drugs, PK parameters follow a similar relationship.

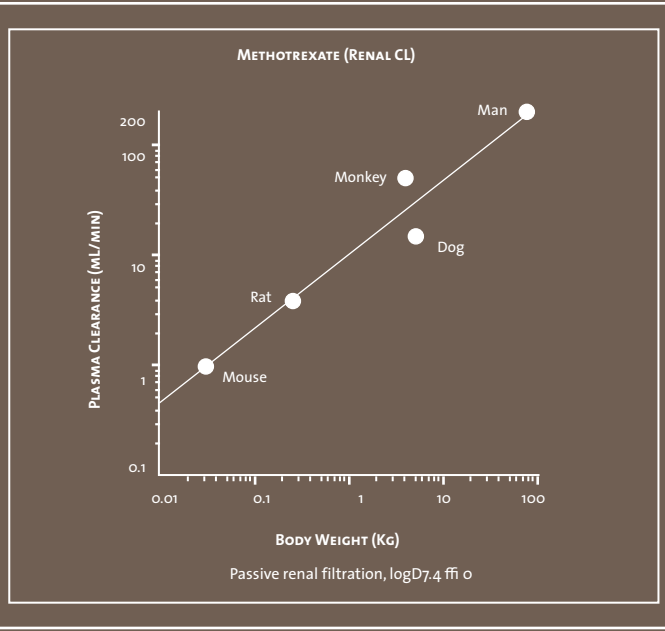
Physiological or PK parameter = $A * BW^{\alpha}$ ... ...(3)

The values of A and the power function (α) depend on the physiological or PK parameters being studied.

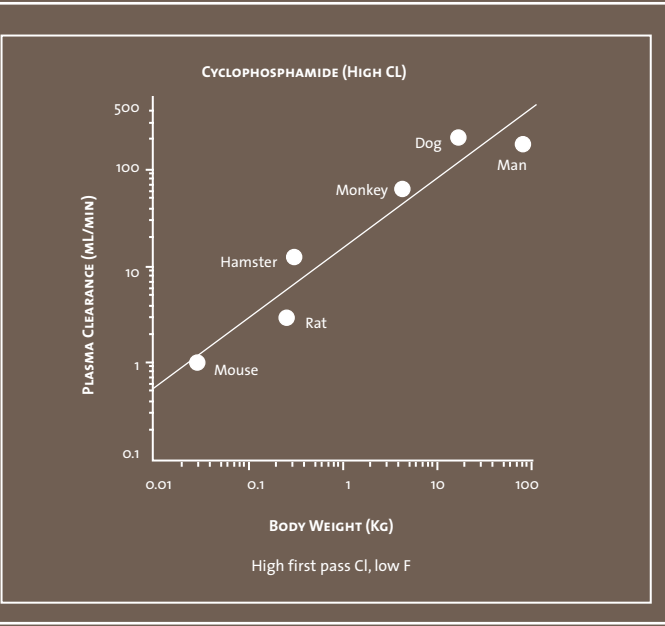
Examples of this relationship are shown for clearance of cyclophosphamide *(Figure 2)* and methotrexate *(Figure 3)* which are eliminated mainly by metabolism and urinary excretion,

respectively. Volume of distribution can also be scaled with bodyweight but whereas clearance tends to scale better with body surface area (BSA; power function ~0.75), the volume term tends to scale directly with BW (power function ~1.0). The approach works well for drugs eliminated by renal excretion or high clearance drugs eliminated by metabolism. Liu and Chen[12] showed that clearance in man was predicted well (average error ≤ 2-fold vs observed values) for some 20 of 31 drugs using the relationship with BSA and BW. It is generally much less accurate for low clearance drugs, particularly when eliminated predominantly by CYP-450 metabolism. Moreover, this *in vivo* approach can be combined with the *in vitro* approach described previously to provide reasonably robust predictions of human PK prior to the first dose to man.

| FIGURE 2: Allometric relationship of cyclophosphamide clearance to bodyweight in animals and man
(Redrawn from R. M. J. Ings, Xenobiotica, 20, (11), 1201-1231, 1990)



| FIGURE 3: Allometric relationship of methotrexate clearance to bodyweight in animals and man
(Redrawn from R. M. J. Ings, Xenobiotica, 20, (11), 1201-1231, 1990)



The preclinical PK and metabolism studies do not stop here. In non-clinical development, the toxicology species have to be shown to be sufficiently exposed (AUC and C_{max}) to the same chemical species (drug and metabolites) as expected in man to provide confidence in the relevance of the safety data to man. Typically, this involves dosing a radiolabelled form of the drug (normally ^{14}C but sometimes ^{3}H) to each of the toxicology species, so that all drug-related material can be accounted for. The recovery of excreted radioactivity (excretion balance) in urine and feces, over an appropriate period based on the anticipated half-life, should ideally be close to 100% of the dose,

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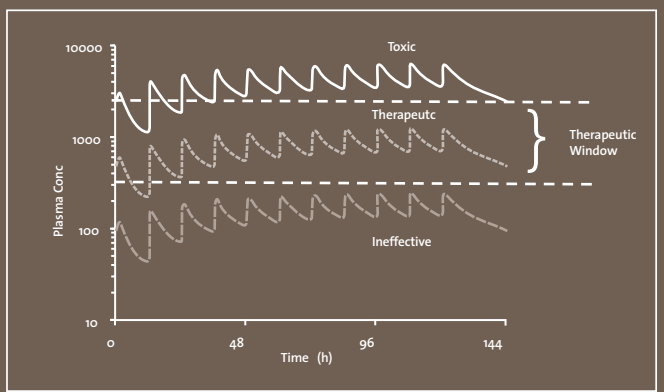
and indicates the extent to which drug-related material has remained in the body. The plasma and/or blood concentration-time profiles of radioactivity can be compared with those of the drug to provide an assessment of the extent of circulating metabolites. Also, if a large amount of radioactivity is found in feces, especially after iv, dosing, a separate biliary excretion study may be required.

The quantitative profile using radioactivity, and identification using mass spectrometry and possibly also NMR, of metabolites in the collected urine, feces, bile, and plasma samples should then be determined. An additional radiolabelled study examines the tissue distribution of radioactivity usually in the rodent species used for toxicology, most commonly by quantitative whole body autoradiography. These data help interpretation of the toxicology findings and allow dosimetry calculations for a human radiolabelled study. Eventually, when there are sufficient clinical data, an excretion balance study, including plasma profiling, metabolite identification and quantitation in urine, feces and plasma, will be performed dosing radiolabelled compound to man so that the data can be compared with those of the respective toxicology species.

3. CLINICAL PHARMACOKINETICS

Dovetailing into the later portion of the preclinical DMPK program with *in vitro* and *in vivo* studies will be the start of the clinical program. Preclinical PK/ADME and toxicology data, should provide a rational estimate for the starting dose and probable PK profile for the first-in-human study. This is primarily a safety study, but should always include PK, starting with a single ascending dose (SAD) and moving to a multiple ascending dose (MAD) study. In the clinical pharmacology program, these studies have the widest range of doses since they are designed to start at a relatively low, very safe, dose and escalate to a point where side effects are seen. Thus, they are the best studies to evaluate linearity of kinetics, to determine if exposure (AUC and C_{max}) increase in a dose-proportional manner. Ideally drug exposure (AUC) should increase dose proportionally but it may increase less than dose proportionally if there is dissolution rate limitation so the extent of absorption decreases at higher doses e.g. griseofulvin. On the other hand, increases in AUC greater than dose

| FIGURE 4: PK/PD relationship for repeated oral dosing of a drug



proportionality can occur when there is saturation of one or more elimination pathways e.g. carbamazepine. This may even lead to formation of a toxic metabolite not seen at lower doses e.g. paracetamol. At the very least it may amplify effects caused by inhibitory drug-drug interactions or disease states. These early PK studies will identify the risk so that appropriate dose escalation regimens can be designed for drugs with non-linear PK.

Also, although these studies are usually, but not always, conducted in healthy volunteers, it is often possible to obtain some measure of the intended pharmacology (PD) which can help in predicting target plasma concentrations for future efficacy studies.

As previously described in this series[13,14] the PK/PD relationship can be summarised as:

- No amount/concentration of drug in the body - no effects.
- Insufficient amount/concentration of drug in the body - inadequate activity and no undesired effects.
- The optimum amount/concentration of drug in the body - appropriate desired activity with low risk of undesired effects.
- Excessive amount/concentration of drug in the body - maximum desired effects but with high risk of undesired effects.

Most drugs are administered chronically and at steady-state the average unbound drug plasma concentration over one dosing interval equals the unbound drug concentration at the target receptor/enzyme site. Thus, plasma drug concentrations can be used to follow the drug concentration profile at the target site. This is summarised in *Figure 4* for repeated low, moderate and high oral doses of a drug and their relationship to the intensity of PD effects.

If the target Css concentration(s) associated with optimal activity and with a low risk of toxicity have been identified, either from *in vitro* or *in vivo* pharmacology data combined with knowledge of plasma protein binding

and/or from PK/PD modeling, effective dosage regimen(s) can be calculated since at steady-state:

Rate in (Dosage regimen) = *Rate out* = CL * C_{ss}

$$= \frac{CL}{F} * C_{ss} \quad \ldots\ldots\ldots\ldots (4)$$

where CL = clearance, C_{ss} = steady-state concentration, F = bioavailability

This offers a more rational basis for dosage regimen design than empirical testing of dose-effect relationships.

An important facet of the clinical pharmacokinetic/pharmacology program is to understand the sources of variability of the PK of a drug in normal clinical use so as to maintain efficacy and minimize unwanted side effects by the rational adjustment of dosage regimen. There are many sources of variability *(Table 2)* and several of them will have already been identified from the *in vitro* studies described earlier.

• Effect of Food

The rate and extent of absorption of some drugs can be affected by food. It can delay gastric emptying and access to

TABLE 2: Factors affecting drug pharmacokinetics and disposition

Factor	Outcome
Dose	Saturation of absorption and/or elimination
Age	Decreased renal, hepatic and respiratory function Decreased plasma drug protein binding
Liver disease	Changes in drug metabolism capacity
Kidney disease	Decreased urinary elimination of drugs, metabolites and endogenous components; decreased hepatic metabolism capacity
Respiratory disease	Increased hepatic metabolic capacity
Heart disease	Reduced blood flow to all organs/tissues with potential effects on drug elimination
Gastro-intestinal disease	Decreased drug absorption
Drug interaction	Modify clearance, increase or decrease steady-state concentrations
Food interaction	Modify rate and extent of absorption for some drugs

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absorption sites in the small intestine and thus drug absorption. A high fat meal shows the largest effect on gastric emptying. Thus, for orally administered drugs a food effect study is usually performed comparing the PK of a drug in the fasted state with that when a high fat meal is given, typically using a crossover design.

The effect on extent of absorption depends on physico-chemical properties of the drug, with high fat meals often enhancing the absorption of highly lipophilic drugs e.g. saquinavir, by stimulating secretion of bile. However, food effects for a given drug may vary, with the absorption of propentophylline decreased and that of spironolactone increased when given with food.

• Effects on clearance

The mean steady-state drug plasma concentration (Css) for total or free drug is inversely proportional to the corresponding total clearance, where total clearance is the sum of the clearance for each pathway i.e.

$$Cl_{tot} = Cl_{renal} + Cl_{metab} + Cl_{biliary} + \ldots\ldots\ldots (5)$$

A change in clearance of any pathway will change total clearance, leading to a change of the mean Css, and ultimately, the PD of the drug. Thus, it is essential to identify the major routes of elimination of a candidate drug in order to predict factors that could impact its total clearance.

This is accomplished using a combination of data from many of the *in vitro* studies described earlier and the data from a human radiolabelled excretion-balance/plasma profiling/metabolite identification study. The latter study will show the major routes of elimination of the drug. If it is primarily renal or biliary (feces) excretion, transporters will play an important role and identifying those involved will allow appropriate clinical studies to be performed evaluating possible drug-drug interactions. Examples of transporter interactions are the inhibition by probenecid of active renal secretion increasing drug plasma levels of penicillins and cephalosporins. Cimetidine and trimethoprim have a similar effect on pramipexole and dofetilide. Also, renal and hepatic function decrease with age and potentially with disease leading to decreased clearance of a drug and increased plasma drug Css in elderly patients and in those with renal or hepatic failure if the dose is not adjusted. Age and disease may also modify the plasma protein binding of a drug, with a consequent effect on volume of distribution and potentially half-life.

Inhibition or induction of metabolising enzymes e.g. glucuronyl transferases, and most CYP450s are well known[15]. Grapefruit juice inhibits CYP3A4/5 decreasing the metabolic clearance and increasing Css of atorvastatin and omeprazole. Cimetidine has a similar effect on diazepam. Ketoconazole inhibition of terfenadine metabolism by CYP3A4, reduced its clearance, increased its Css, and led to its withdrawal from the market because of the resulting QTc prolongation, torsades de pointe and death in some patients. Inhibition of metabolism of a drug by another can also be used therapeutically to reduce its clearance and prolong its duration of effect e.g. ritonavir has this effect in HIV drug combinations. Enzyme induction can increase levels of some metabolising enzymes e.g. CYP3A4, CYP2C9, glucuronyl transferases. Carbamazepine and rifampicin induce CYP2C9, CYP2C19 and CYP3A4, and can thereby increase the clearance, decrease Css of many drugs metabolised by these enzymes.

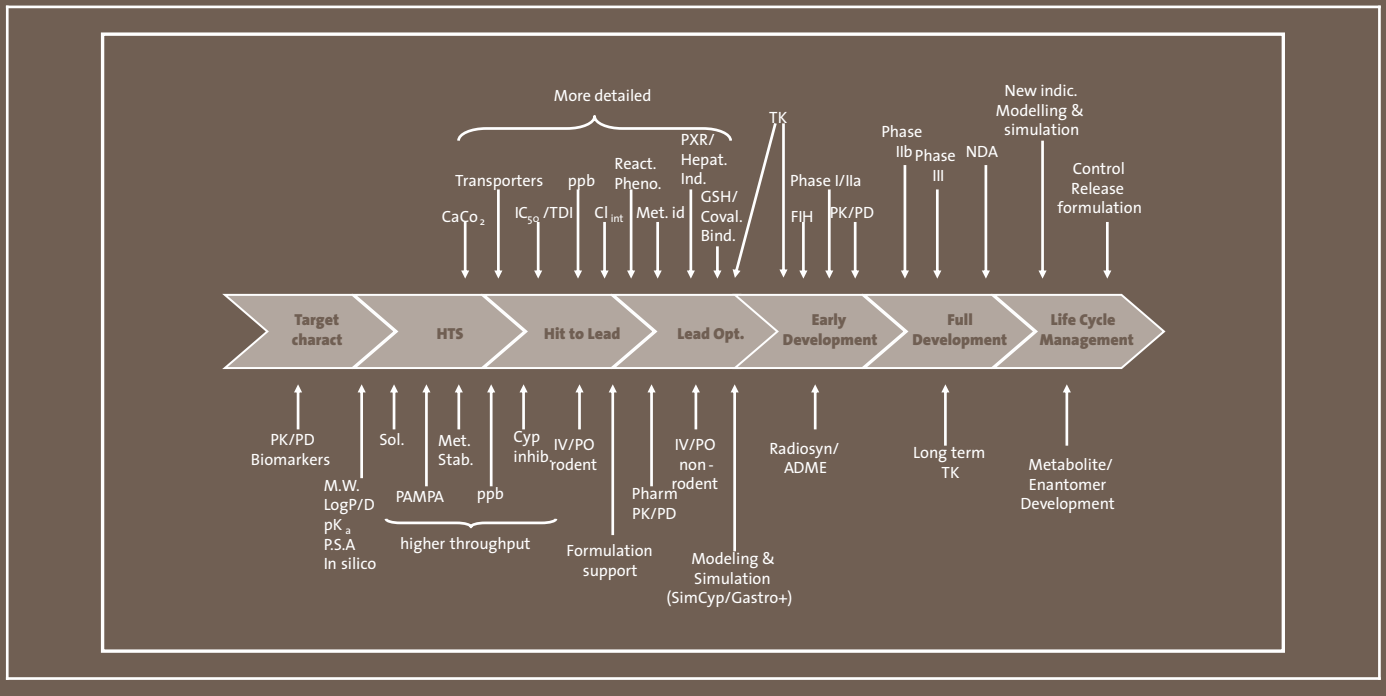
Thus, one of the important aspects of any clinical pharmacology program is the identification and mitigation of possible drug-drug interactions. There are two facets to this, the first being a co-administered drug interacting with the candidate drug where the latter is the victim and the second is the candidate drug interacting with a co-administered drug where the candidate drug is the perpetrator.

When evaluating drug-drug interactions where the candidate drug is the victim, identification of the *in vivo* human metabolites from the human radiolabelled study combined with the data from the reaction phenotyping studies are used to quantify the extent of transporter and/or enzyme involvement in the elimination of the candidate drug and which enzyme(s) is associated with the production of individual metabolites. All major pathways (>25% of the total clearance) should be evaluated with appropriately designed *in vivo* clinical studies, usually under steady-state conditions, using either a known strong model inhibitor/inducer or a known strong inhibitor/inducer that is likely to be co-prescribed. If there is a clinically significant interaction, recommendations should be made on the appropriate dose adjustment or drug exclusions.

When evaluating if the candidate drug is a perpetrator of a drug-drug interaction, *in vitro* data are again used as a guide as to what *in vivo* clinical studies are required. If the candidate drug is found to be a strong inhibitor or inducer of a specific CYP-450 or transporter, appropriately designed *in vivo* clinical studies should be performed either using model substrates or drugs that are known substrates that are likely to be co-administered. Again, recommendations should be made as to whether to avoid co-administration of drugs or dosage regimen adjustment where such interactions are shown to be clinically relevant.

Despite all the studies described above, this not the end to the understanding of the clinical PK and PD of a candidate drug, as other sources of variability can occur such as gender, weight, ethnicity, disease severity, genotype (e.g. CYP2D6), various physiological parameters (e.g. creatinine clearance) and unanticipated drug-drug interactions. Although many of these can be examined using separate traditionally designed studies, they can also be investigated using a population PK approach with sparse plasma sampling from the patient population participating in the Phase 2 and Phase 3 trials, examining the factors of interest as covariates and using Bayesian feedback to optimize dosage regimen. However, to use this approach, the

| FIGURE 5: A summary of the input of drug metabolism and pharmacokinetics in the drug discovery and development process



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studies must be designed prospectively with the appropriate experimental design built into the protocol to ensure the true dosing history, sampling times and covariates are accurately recorded, even if they deviate from protocol.

Once all the non-clinical and clinical PK/ADME data have been obtained they will have to be collated, interpreted and summarized in the respective regulatory marketing authorization (e.g. NDA, MMA) documents. It is key, when preparing the clinical pharmacology section to ensure that all aspects of the clinical pharmacology, including relevant *in vitro* assays such as the plasma protein binding, cytochrome inhibition, cytochrome induction, reaction phenotyping, transporter substrate/inhibition are adequately described and not just the *in vivo* clinical pharmacology so that the reviewer is able to follow the rationale of the clinical pharmacology program.

4. CONCLUSIONS

As can be seen from the overview above and from *Figure 5,* PK impacts all stages of the discovery and development of a drug. This input does not stop after approval of the NDA/MMA, but continues into life cycle management with novel formulation development, new indications with possibly different dosage regimens, new dosing routes and even the development of active metabolites or a single enantiomer where appropriate, perhaps in a different indication.

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An interactive, modular course providing broad knowledge-based learning across the specialty of pharmaceutical medicine; run by BrAPP working closely with Cardiff University.

Modules are mapped to the syllabus for the UK Diploma in Pharmaceutical Medicine exam.

Ten two-day, non-residential modules run in central London from January 2016 to July 2017. (The exception is Module 1 which is held at Cardiff University.)

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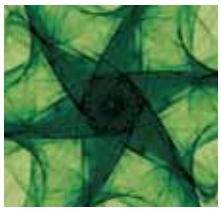
MHRA CASE STUDY:

MSD successfully put their advanced new melanoma treatment through MHRA's early access to medicine scheme (EAMS).

From: MHRA December 2015



THE CHALLENGE

SPEEDING UP PATIENT access to new, promising, innovative treatments is a current priority for the UK government, regulatory agencies and the pharmaceutical industry.

MHRA's early access to medicines scheme (EAMS) aims to offer patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need.

MSD (known as Merck & Co Inc. in the United States and Canada), works to address unmet health needs through the development of innovative medicines, vaccines, biological therapies and animal health products. Pembrolizumab was being developed as a treatment for advanced melanoma (skin cancer), where MSD had identified an unmet clinical need.

Through EAMS, MHRA has been able to work with MSD to ensure that UK patients with advanced melanoma have been among the first in the world to access the breakthrough treatment, pembrolizumab. This has enabled approximately 500 patients with advanced melanoma with limited treatment options to benefit from the treatment prior to licence and paved the way for accelerated routine access in the NHS.

In June 2014, phase 1 clinical trial data published by the American Society of Clinical Oncology (ASCO) pointed to the significant health improvements exhibited by patients who had been provided with pembrolizumab as treatment for advanced melanoma. These exciting results helped to confirm that pembrolizumab could address an unmet medical need.

However, patients who required the treatment would need access to pembrolizumab in the intervening time between clinical trials completing, when the treatment meets with regulatory approval and is licensed, and when the treatment is finally available for routine use – a process that can often take several months and that can affect seriously-ill patients who cannot afford the time to wait for treatment.

In October 2014, MSD requested that MHRA consider accepting pembrolizumab into EAMS and worked with a series of co-ordinated stakeholders to progress their treatment through the scheme, including: MHRA, National Institute for Health and Care Excellence (NICE), NHS in England, Northern Ireland, Scotland and Wales.

HOW MHRA HELPED

MSD was clear about the intrinsic benefits EAMS offered. However, as the first medicine through the 2-step process, there were a number of practical issues that required interaction between MHRA and MSD to ensure that the review was concluded within the expected timeframe. These included:

- reviewing pembrolizumab against EAMS criteria to ensure it was a suitable and acceptable candidate at the face-to-face pre-submission meeting

- condensing the timelines around awarding the promising innovative

MHRA CASE STUDY:

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medicine (PIM) designation and the assessment of the scientific opinion step, which helped to reduce the overall duration of the process and ensure the right resources were allocated at the right time

- offering availability for regular interactions with the EAMS assessment team, to help with data reviews, speeding up analysis and interpretation

- agreeing to be flexible and accept summaries of data that MSD was already preparing for their licence application dossier, rather than re-writing and submitting specifically for EAMS, helping to reduce the burden of the submission

- clarifying pharmacovigilance criteria and future regulatory requirements.

Ben Lucas, Business Unit Director, Oncology, MSD said:

EAMS undoubtedly accelerated access to pembrolizumab for patients with advanced melanoma and demonstrates a world-leading example of how healthcare agencies and industry can work together to get treatments to patients more quickly.

We're proud of what we achieved: early patient access to our breakthrough treatment, as well as extensive collaboration with MHRA, NICE and NHS England, and industry firsts – in participating in and helping to develop EAMS, and in being awarded the first positive opinion.

THE OUTCOME

EAMS has enabled approximately 500 advanced-melanoma patients in the UK to be among the first in the world to benefit from access to pembrolizumab ahead of a European licence, indicating the value of fast-tracking innovative medicines so that they reach patients with high unmet medical need more quickly.

Submission through EAMS accelerated patient access to the treatment by around 4 months. Early engagement of stakeholders through the scheme secured priority scheduling from NICE for review. Important milestone dates include:

- 10 October 2014: PIM designation awarded

- 9 March 2015: MHRA issued Scientific Opinion for pembrolizumab through EAMS

- 17 July 2015: European Commission (EC) granted an EU licence for pembrolizumab which marked the trigger for the closing of EAMS to new patients - existing EAMS patients continued to gain access to the medicine until routine reimbursement

- 29 July 2015 - first NICE appraisal committee meeting for pembrolizumab in treating unresectable, metastatic melanoma after progression with ipilimumab

- 7 September 2015 – NICE final appraisal determination (FAD) guidance recommended at the shortened 30 day implementation, down from the standard 90 days

Pembrolizumab was the first medicine to be awarded an EAMS positive scientific opinion by MHRA. The application procedure with MSD helped to identify and resolve some practical issues including data content, appropriate labelling, optimising timelines, clarification of pharmacovigilance requirements and appropriate monitoring and risk management.

Learning these lessons has helped to refine EAMS and to demonstrate that the scheme offers a genuinely accelerated process for patients in the UK to access new medicines that work to satisfy unmet medical need, as well as showing that UK health agencies can offer a very streamlined process that supports early access to critical treatments.

MHRA CASE STUDY:

MSD successfully put their advanced new melanoma treatment through MHRA's early access to medicine scheme (EAMS).

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Dr Siu Ping Lam, Director of Licensing, MHRA said:

EAMS is an important step in ensuring patients gain access to innovative medicines as soon as possible, improving health outcomes in patients that urgently need new treatments. MSD's decision to submit pembrolizumab meant that we awarded our first positive opinion ahead of a licensing decision, thoroughly tested EAMS' principles and processes, and learned much along the way.

HOW CAN WE HELP YOU

Contact the *Innovation Office* to find out more about accessing expert knowledge, guidance and experience that could help you develop ideas and save time and money
#HealthInnovation

EAMS aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. *Visit EAMS* to find out more and how to submit your medicine.

Dr Mark Edwards

Many of you know Dr Mark Edwards in his ongoing capacity as the Ethical Medicines Industry Group (EMIG) R&D Director.

The Global Medical Excellence Cluster (GMEC) is a not-for-profit company formed by its founder universities to develop a framework within which universities, commercial organisations and National Health Service Trusts can collaborate to accelerate progress in Translational Medicine, bolster the UK's globally competitive position in biomedical research, attract inward investment and improve patient outcomes.

Founded by five of the world's top universities, Cambridge University, Imperial College London, King's College London, Oxford University and University College London the company was joined by Queen Mary University of London in 2012.

GMEC is open for proposals from healthcare companies to devise and implement projects which will create new cross- sector opportunities in biomedical research.

Dr Mark Edwards

GMEC wishes to announce that, after six years in the role, Dr Jim Hagan is stepping down as CEO of GMEC to pursue other interests and will be replaced by Dr Mark Edwards, who has been appointed Interim Executive Director. Reflecting on his time as the founding CEO, Jim commented "The life sciences are critically important to the health of the nation and the economy and it has been a privilege to work with the shareholder Universities of GMEC on initiatives which delivered real value in both domains. Our work in helping to establish Imanova and the GMEC-Pfizer Rare Disease consortium shows what can be achieved when these great Universities work together. I'm extremely grateful to the GMEC Board for their support and to have had the opportunity to work with so many outstanding people during my time at GMEC. I wish Mark every success in taking the company forward."

On behalf of all the GMEC members, the Board expressed sincere thanks and appreciation to Jim for all his efforts and commitment and welcomed Mark to the Leadership team.

MEETING REPORT:
8th BrAPP Education Day,

26 November 2015

Report by Liz Langley

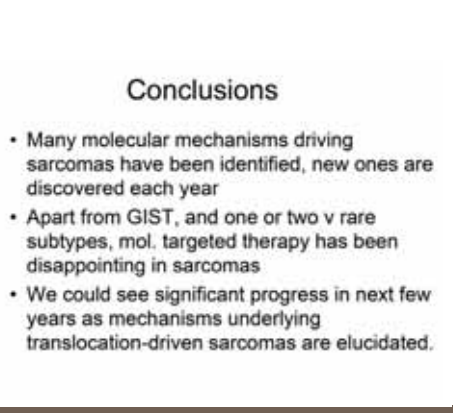
IN 2008, THE then BrAPP committee sat down to discuss our meetings programme in the light of anticipated revalidation and the CPD imperative. It resolved that those "in" education ie HMT (as was) were well served but the remaining majority and perhaps independent physicians in particular might find it difficult and expensive to maintain their training portfolios.

Training, education and development are the main platforms for BrAPP's activities and the committee felt it was important to develop an annual one-day, cost-effective "Hot Topic" meeting which would be attractive to busy physicians. And so the BrAPP Education Day was born. One of the leading exponents of the event was a then very new pharmaceutical physician called Anne Appleton.

It is therefore fitting, if very sad, that the 8th Education Day should see the delivery of the first Anne Appleton Lecture following her sad death in April 2015. **Professor Ian Judson,** a global expert on sarcoma, who had met Anne on a number of occasions at the Royal Marsden agreed to give the inaugural lecture.

Members and colleagues gathered at a new location for the meeting. Not our usual college environment but perhaps one better suited to the fast moving and innovative industry and one that BrAPP is using to deliver the London modules of the PostGraduate Course in Pharmaceutical Medicine.

Prof Ian Judson rather provocatively entitled his lecture **"Molecularly targeted therapy for sarcoma – has it fulfilled its promise?** His subtitle was **"Is there a magic bullet?"** and the brief answer to that is "no". Sarcomas are rare malignancies of connective and other non-epithelial tissue and their chief characteristic is heterogeneity. Their aetiology remains largely obscure and, although some risk factors have been described and are largely associated with mutation of DNA, only 3 out of 500 mutations identified can be



Prof Ian Judson

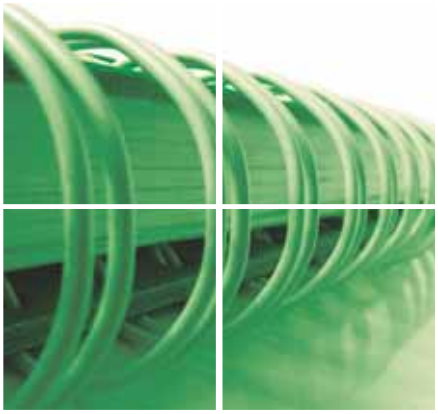
said to be actionable. In other words the majority, as yet, seem not to be useful for targeting purposes.

Imatinib is known to highly effective in advanced GIST (gastrointestinal stromal tumour) and mean survival rates have been extended to 6 years. This compares extremely favourably with the previously used and essentially ineffective doxorubicin therapy. The newer therapies also have patient benefits too because shrinkage of tumour often occurs very quickly thus improving comfort and well-being. The latest molecule, regorafenib is proving useful as a 3rd line rescue therapy extending relapse-free survival (RFS) rates in advanced patients from less than one month to 5 months. Used as adjuvant therapy, Prof Judson stated that there is a survival advantage of up to three years compared to one year on single therapy regimens. He suggested this is a REAL advantage and this is reflected by NICE approval. Regorafenib currently remains available via the Cancer Drug Fund but its future is questionable. What concerns researchers is the regulatory authority "obsession" with median survival rates and the apparent desire of the industry only to develop "blockbuster" medicines. Judson says that it must be accepted that patients will die and so clinicians must have the ability to select which patients, to their knowledge, are likely to do best on such regimes. Selection of suitable patients may assist the cause of availability.

Patient care and well-being was stressed throughout. Prof Judson's frustration that the development of scientific theory, followed by identification of specific changes at molecular level and then the much needed proof-of-concept are parts of such a long process often without a positive result was plain to hear. He cited an example of the time lag in the case of translocation driven sarcomas. These were first identified in 1987. In 1995 researchers revealed that they had something to do with transcription of cellular DNA. It was not until 2013 that the process could be properly described. In that period of time useful agents can come and go. In the case of Ewing's Sarcoma, another rare bone condition which affects children and adolescents, IGF-1R has been found to deliver amazing (Prof Judson's word) results – albeit short-lived. When used with linsitinib early studies looked good – until the IGF-1R ran out. When IGF-1R was shown to be ineffective against lung or colorectal cancer, pharmaceutical development ceased and experimental supplies soon ran out. Prof Judson believes that if only there had been time to understand how IGF-1R worked in Ewing's Sarcoma it could have been a life-saving drug.

For many of us the humanity and humility of the presenter shone through especially as the biochemistry became

David Watson



more impenetrable. The relatively small numbers of patients affected by sarcoma and the heterogeneity of the conditions are currently commercially unattractive. But this does not quench his desire to find answers for his patients. Prof Judson does feel that we may be on the cusp of new understanding as translocation increasingly appears to be a primary aetiology of many sarcomas. His clarion cries were for a) more biochemists to work deep within the Kreb's cycle and other loci which might affect chromatin regulation, b) pharma of whatever size to engage to supply medicines whether or not they will ultimately be profitable and c) clinicians to listen to their patients.

After a reflective break, **David Watson,** ABPI Director of Pricing and Reimbursement brought us back to the hard reality of money. His presentation title, **Value, Access and Reimbursement,** has been a recurring one for BrAPP Education Day. David gave us a useful overview of the current NHS structure remarking that whilst our global pharma colleagues may be under the misapprehension that there is one system in play the reality is far more complex than that! For example, there are between six and ten thousand

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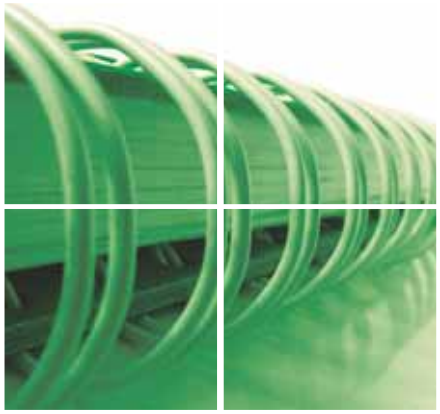

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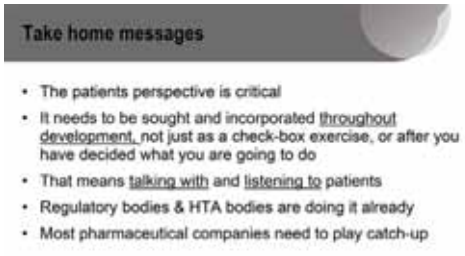
people employed by NHS England alone (85% of the system) involved directly in Medicines Review. Centralised it is not.

In November 2014, the Government's Office for Life Sciences announced the Accelerated Access Review (AAR) initiative to recommend how to get innovative medicines and technologies to patients as quickly as possible. An interim review was published in October 2015 but it did not define the pathway for access to new products nor is it yet clear how "transformative medicines" will be paid for. It is anticipated that the mandate of NICE will be revised sometime in 2016 on the back of the AAR. This will perhaps lead to a conditional approval system in which assessment of cost will play an increased role.

Patient access to new medicines is the political imperative but currently it is felt that very few new introductions will get immediate (list price) funding and companies will have to develop creative and transparent arrangements with the NHS to enable usage. The published findings of the Cancer Drugs Fund (CDF) Consultation highlighted the need to review access and funding right across the board. (reference: Operations of the CDF 2014/15 Consultation Report. NHS England. November 2014). There was some dissonance between industry responders and other participants in the published consultation. The 2015/16 consultation is currently underway. The CDF is generally regarded as a political sticking plaster and industry's view is that it probably should not be necessary.

David would contend that most of industry's customers in the UK do not understand pricing. They tend to believe that medicines come to market with the highest price and will, when pressed, be negotiated downwards. Perhaps not the best position for collective and cooperative working between supplier, assessor, commissioner, prescriber and end-user. David then reminded us of the current PPRS mechanism. The 2014 PPRS which runs until 2019 is very different to previous schemes. One of the drivers ahead of negotiation was a desired double-digit cut in prices by the Government. The outturn allowed free pricing at launch, no price cuts, a growth in the medicines bill (with exclusions) underwritten by industry at agreed rates. It also agreed the maintenance of the status quo re NICE. NICE would not determine price or lower thresholds for use. The money "going back" to the Government, however, does not appear to be improving access or uptake and industry is now seeking to improve the system.

David responded to a number of questions or comments from the floor. Whilst he hoped that the AAR would produce useful outcomes he cautioned



Dr Paul Robinson

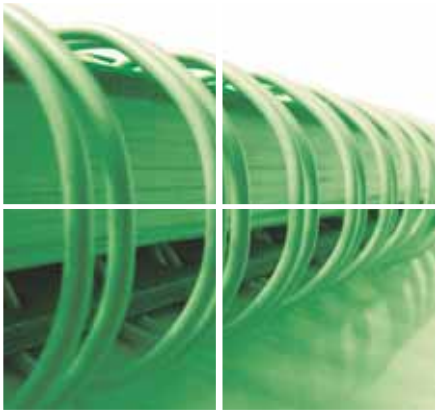
that truly centralised decision-making might risk a reduction in competitiveness and the effective locking-out of any second-to-market medicines.

Dr Paul Robinson's presentation was entitled **"When all else fails .... go ask the patient!"** His slides presented a number of case studies in which the patient-viewpoint, collected in detail and early in development, may have influenced the decision-making process for the benefit of all parties. These included the impracticability of inhaled insulin in everyday usage, the preparedness of patients to understand and accept risk when a medication solves a condition which severely impairs normal daily activity, and the acceptance by patients of relatively small but sustained weight loss via use of an implantable device despite a possible higher risk profile for the implant. The first was licensed after 10 years development with huge industry expectations but voluntarily withdrawn after 9 months, the second was initially withdrawn but later reapproved after patient feedback and demand and the third was approved following an FDA-sponsored survey of patient preferences. And it is not only the FDA taking an interest in patient opinion. The EMA published a document called "Working with patients and consumers" in 2015. Paul's point to his fellow industry professionals was that we should not get left behind. He showed the audience a 2-minute video from Patient Research Exchange which illustrates that thinking https://vimeo.com/128992520

In keeping with the original idea of Education Day, we welcome some on-going presentations and that from the PMCPA is one of those. This year, **Heather Simmonds** who stepped into the breach to present **2016 Code of Practice**. Heather talked about the work of the Review Group and reminded us that an assessment of the clauses to retain was also accompanied by a process to simplify and delete content where this improves the functionality of the Code. Over a period of time the ABPI Code is also being brought into line with the EFPIA Codes as well as UK law, MHRA Blue Guide, plus other regulations. The change to single signatory in the forthcoming edition is a case in point. Certification will not be required for Joint Working agreements nor for contracts with patient organisations. Clause 26.5 (Relations with the Public) is deleted from the 2016 Code and all representatives employed after October 2014 must now sit an accredited examination. Disclosures and transfer of value with regard to Health Professionals and Healthcare Organisations are also procedurally tightened with defined reporting times. Companies are also required to publish a summary of the methodologies used to prepare disclosures. In a candid moment, Heather revealed that the disclosure data goes live on the central platform by 1 July, she believes the early summer 2016 is going to be very busy at the PMCPA.

We took a little time to review some published cases from 2015 to usefully illustrate current issues and finally Heather reviewed a number of the other activities of the PMCPA. She highlighted Advisory Boards and the UK Sunshine Rule which comes into force in 2016 and further seeks to increase transparency amongst HCPs in relation to their industry interactions.

Heather Simmonds



Bina Rawal is also a regular delegate and speaker at Education Day and this year came to follow up on one of her particular spheres of interest – **the EMA and Clinical Trial Transparency.** It seems a long time since Ben Goldacre published Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients. In fact it is little more than 3 years ago. The new EU Clinical Trials Regulation (EUCTR) was published on 27 May 2014 and it seeks to streamline processes via the new EU portal and EU database including increased transparency on clinical trials and their outcomes. The development of the portal and database have proved challenging. The most recent meeting of the EMA Management Board in October 2015 reported that, following significant trials and subject to successful independent audit at the end of the third quarter of 2016, it expects the Regulation to come into application by the end of 2017. From that point onwards sponsors and Members States will use it for all new clinical trial applications in the EU and the information from the database will be publicly available.

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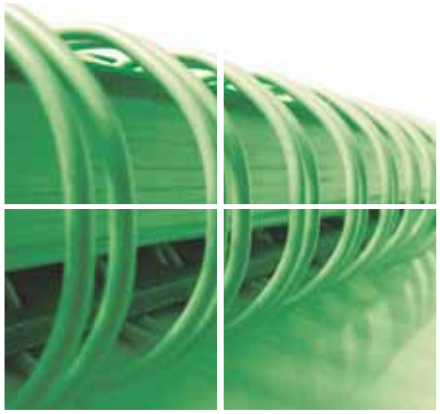

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Meanwhile EudraCT – the database for all clinical trials commenced in the EU from 1 May 2004 – is enshrined in legislation and continues to report on a monthly basis. Provision of results became mandatory from 21 July 2014. Studies which ended prior to July 2013 must be entered by July 2016. The posting date is considered to be the compliance date and three months after the anticipated due date studies with overdue reporting will be publically highlighted. Each version of the data entry will be stored and new postings will NOT result in deletion of the previous versions. Adult Phase 1 studies, not part of a PIP, do not have to be made public retrospectively. Looking forwards all summary results must be published within one year of completion (6 months for paediatric studies). A lay summary is required for all studies and all must be submitted regardless of outcome, including terminated studies. Deferral of publication of trial information may be requested until 12 months after the end of trial but it must published along with the summary of results. Deferral must be justified on the grounds of serious commercial risk etc. Redacted clinical study reports (CSRs) must be published 30 days after marketing authorisation approval (MAA).

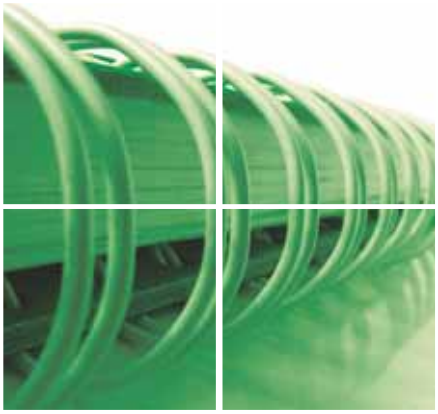
It is anticipated that first sets of CSRs will be published in 2016 – all redactions must be approved by EMA.

Bina Rawal

Phase 2 of the data release will seek to publish anonymised individual patient data but this phase is currently delayed and the details of the process are yet to be fully fleshed out. Sponsors should note that the default position of the EMA is that nothing is confidential or commercially sensitive so any redactions need to be legitimate. Access to the data is stratified and it is given that users must not use information for unfair commercial reasons or to identify patients/individuals. A level 1 of access, members of the public having made a suitable declaration obtain a user ID and password. They will then be able to see CSRs in a searchable view-only mode. At level 2 of access, bona fide academic researchers provide more detailed information about themselves which if approved will allow CSRs to be downloaded, saved and printed. Using ICH E3 format for CSRs it will be important for sponsors who wish to redact to be very clear that their requirements meet the expectations of the EMA.

Sounding similar in process to drug safety/pharmacovigilance reporting timelines or the ticking clock of regulatory approval, sponsors have another set of critical mileposts to satisfactorily negotiate before a new drug can successfully come to market in the EU.

Sarah Eglington, Healthcare Intelligence Director at Binley's Wilmington Insight, and her team have recently conducted a research project entitled **"What healthcare professionals think of the UK pharma industry".** Market research is not an area that pharmaceutical physicians and other industry professionals feel very comfortable with. Validity and relevance are always important. Market research can give direction to further customer relationship building. Based on 2000 responses and conducted independently, the report has some useful insights into opinions in the marketplace.



GPs said they were generally under pressure (although they still participated in the study) with 40% of respondents claiming that the pharma industry as a whole was poor at understanding the challenges they faced. 74% of responders claimed never to visit company website and 83% never used apps of any kind with their patients. Overwhelmingly (84%) they thought their biggest challenge was rising patient expectations. 66% of responders claimed not see representatives.

Their practice managers felt the pressure of patient expectations too (87%) and also thought that industry could help more through funding of specific personnel (medicines management facilitator) but more broadly through training for practice staff. The practice nurses, on the other hand, were more forthcoming and considered themselves in need of training and prescribing information created specifically for their use. This kind of support requirement was echoed by the NHS manager cohort who felt that industry could provide sponsored nurses (not a new idea), general training for HCPs and reduced prices for medicines. This group identified limited resources as their biggest daily challenge (75%). Hospital doctors were apparently more receptive to the efforts of industry with 40% saying industry understood their problems but within a portmanteau of concerns (75%) felt tired of the NHS being used a political football, wanted new drugs to be added to formularies and wanted more training and opportunity to attend courses. Specialist nurses felt industry had a role in providing patient information but also this group thought it could do better in understanding how patients feel about drugs. Pharmacists broke naturally into retail (not participating in numbers in this survey and saying they need incentives to see pharma reps) and hospital (wanting sponsored education form industry with 47% of responders believing that industry understand secondary care well).

Essentially, Sarah, suggested there were four main areas of focus for industry;

- Partnerships not products
- Educational support and delivery
- Sponsored learning and meetings
- Mutual respect and understanding of each other's aims and objectives in the transaction

The research data suggests there is an opportunity for industry not only to get better but to be perceived as better – surely a goal to strive for. Binley's report will be published soon and repeated in years to come.

The final session of the day was delivered by **Ralph Carter** of PharmaReview. Just how much time does industry and the Med Affairs Team particularly spend on reviewing copy? In a nutshell the answer was too much. Entitled **"Copy Review: An industry within the industry",** Ralph reported on his benchmarking studies with clients in 2014. Surprisingly highly qualified and well-paid professionals (physicians and pharmacists) in Medical Affairs are spending around 45% of their time working on copy. Brand managers claim only to be spending 25% of their time. The same Medical Affairs people say that just under 50% of the jobbags "go round again"

Ralph Carter

compared with less than 40% for brand managers. The impact of reworking copy creates friction, leads to late working, missed deadlines and cost over-runs. It does not build good and rewarding interdisciplinary working relationships.

One of the saddest aspects of this presentation was that despite all the advances of Zinc etc little has changed since to days of the lowly manila folder which was hawked physically around the various collaborating departments of the company. Too much expensive executive time is wasted providing opinion but not taking responsibility. Involving a sensible (small) number of opinion formers and decision makers early on does not appear to happen and the world and his wife like to have a dabble. The agency may go off on frolics of their own rather receiving a definitive brief which is accompanied by all the supporting material – messages are surely generated from the evidence so why not provide the evidence upfront.

Ralph was keen to advocate smaller numbers of decision makers who take

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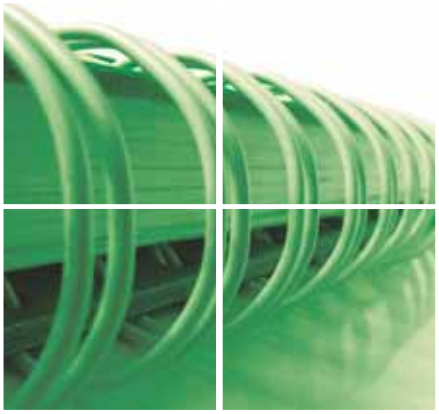

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absolute responsibility for each job. This might mean it will go wrong on occasion but if the person who owns the job is forced to decide, definitively, on each comment the debate and the opportunity to "go round again" should fall away. The right person does need to be in the right role so once again this puts pressure on up front. And they need to be trained. Ralph offered the audience a top seven take home proposals:

- Ensure quality is high before the job enters the system
- Work closely with the agencies and agree service levels
- Work on consistency of review criteria and standards
- Hold planning meetings for big items and major campaigns
- Reduce the number of reviewers
- Define reviewer roles
- Close the feedback loop before it goes back to the agency

How simple it sounds and how long has the industry been striving to get this right. New Year's resolution – let's all try harder and smarter.

A great day, enjoyed by all. Thank you to our speakers and see you all next year.

PROFESSIONAL DEVELOPMENT:

Benefits of being a medical assessor at MHRA

From the MHRA

MHRA HAS LAUNCHED campaign to show people what's involved in the medical assessor role, including experiences from current assessors.

In November 2015, the MHRA launched a campaign highlighting what medical assessors do and the difference they make to public health. The campaign aims to attract people with a medical background considering a career move.

Medical assessors play a key role in medicines licensing and post marketing surveillance ensuring medicines are as safe as possible for patients and deliver their intended benefits.

Staff at MHRA say that variety is one of the main positives of the role. Kirsty Wydenbach, Medical Assessor, said:

"The timelines we work to are very short in the clinical trials unit, but this means no 2 days are the same: one day it's a trial for a new cancer agent, the next it's the latest gene therapy product."

The roles the MHRA offer can involve all aspects of the regulatory process, including making decisions and advising industry.

Another medical assessor Dr Dervla Quinn was previously a GP trainee and clinical pharmacology physician. She says the diversity of work includes "reviewing both potential and confirmed drug safety issues, preparing reports based on safety issues, presenting at UK expert committees, collaborating with colleagues from other European regulatory agencies…"

See what other medical assessors have to say about the role and find out about the benefits of working for MHRA and see available vacancies visit *https://mhramedicalassessors.pgtb.me/86flvg* for more information.

As the medicines regulator, MHRA offers a unique experience in the UK and assessors gain an early insight into medical research, new medicines and new uses for existing medicines.

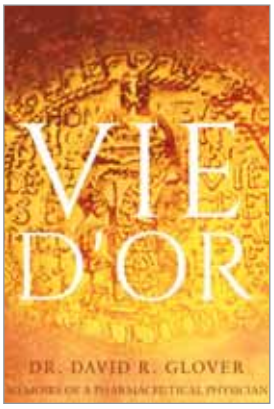
The agency also offers employees training opportunities to excel in their role - for example some medical assessors are now members of the Faculty of Pharmaceutical Medicine. As a medical assessor you are helping to shape the industry from the inside out.

MHRA
Regulating Medicines and Medical Devices

VIE D'OR: MEMOIRS OF A PHARMACEUTICAL PHYSICIAN.

David R Glover
Matador 2015 ISBN 978 1784623 111
Kindle version (£9.99).

Pharmaceutical industry memoirs are like buses, you don't see any for ages and then suddenly two come along together. In the last issue of PP, Ron Stark's entertaining and insightful volume From Farms to Pharma was reviewed and now is the turn of David Glover's tantalisingly titled book, Vie d'Or. Before venturing forth, I should say that the reviewer was privileged to work with both authors whilst they were imparting the benefit of their experiences to new recruits to pharmaceutical medicine. They are tremendous communicators and first-class exponents of our relatively young specialty. These books are good reads.



In reflective mood towards the end of his memoir, David, offers us some thoughts on just how golden his life in medicine and in particular the twenty years of full time employment within the pharmaceutical industry actually was. Like us all he can clearly identify the many highlights, launching new useful medicines, learning new science as biotechnology takes hold, building teams that really work together and for the common good and on acquiring and developing a unique skills set which brought fulfilment, frustration and ultimately a little fame. He also recounts with a degree of candour that only a successful career and an enjoyable retirement could safely allow some of the less enjoyable aspects of corporate life. Surviving these and making one's mark are attributes of great benefit to all aspiring pharmaceutical physicians and David gives the reader the chance to see how he steered his career towards good outcomes. He looks back and remarks in hindsight that a different dosing regimen might have seen a drug be more successful in development phase and on the other hand how the cut and thrust of venture capital world and floating on the stock market add extra flavour and excitement to an already hugely varied medical career.

Vie d'Or is a very personal memoir and offers us an insight into the minutiae of life in industry too. It is none the worse for that. From a traumatic bout of food poisoning at the end of an international meeting held in the UK on the one hand, nearly meeting his maker in a taxi in Seattle and the degree of disgruntlement amongst non-invitees to an award ceremony on the other; these are the joys. David has had the resilience to grow his career, makes friends along the way and not to be bruised by any misplaced slings or arrows.

The text is peppered with entertaining pictures and cartoons much as were David's training presentations. Running has always been an important part of his life and I am sure the delegates at one particular BrAPP Survival Guide will recall an early evening workshop

session conducted in Lycra! He was never boring and Vie d'Or makes that very clear. Joining MSD in 1984, David argues that he may have enjoyed the heyday of the blossoming industry but for those us who remain and those of you to come it behoves us to keep the banner flying. This book may help you reflect on ways to do that. There is no spoiler in this review – you need to read the book to discover from what its title is actually derived. A clue – we wouldn't get away with now!

Mrs E Langley

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Mission Complete

By Hugh Gibbons

FIFTY YEARS AGO this very month, I met my first pharmaceutical physician - when I joined Riker Laboratories (a precursor of today's 3M Healthcare) in Loughborough.

Eric was typical of the many affable members of medical departments I encountered over the next three decades or so. Offset by a few banana-heads.

I'd spent two years as an advertising writer at Notleys, a leading London agency famous for its creativity and poets on the payroll; in an office shared with two designers, the novelist William Trevor, and an executive's usually continent corgi, parked for the day under our desks. As the only job applicant turning up with a pen, at Riker I was a shoe-in for Chief Copywriter in Marketing.

My new office home appealed. Allegedly a former sock factory, it had wavy wooden floors where machines had clacked energetically for decades. From the big windows there was the Grand Junction canal and coal-dust-spiked sunsets over Charnwood Forest on one side, and a vista towards rural Leicestershire on the other. On Streetview it still looks a cheerfully characterful head office.

I found it a warm-hearted workplace, where people made time to talk face-to-face and share their family and local community lives beyond the office. They were proud that Loughborough is the home of Taylor's, the world's biggest bell foundry, whose work you can hear in the town's carillon and St Paul's Cathedral. And in Clemerson's furniture department Nick Alkemade was to be found, famous for falling 18000 feet without his RAF parachute on to a snow-covered forest.

Just a leg sprain, since you ask. And PTSD.

Unlike socks or bells or sofas, pharma products are rarely seen by their office staff. But one day I found a cache of small packs hidden behind a radiator, presumably stored for some private enterprise marketing. They were GP samples of, ahem, Durophet-M - the phet reflecting the main ingredient. Fetching a pound a capsule down the pub, Eric said...

The world of office work had a few significant differences from now. Most noticeable, no keyboard or screen on your desk. For document production, many executives shared an Audiotyping Pool. You dictated thoughts into a tape recorder and took the cassette along to Edith, in charge of the team of typists (some of whom doubled up as babysitters). She'd sometimes have to remind you to ask for 3 carbon copies at the beginning of the tape rather than the end, please. But dictating gave you the long-lost benefit of hearing the words, and speaking short sentences, and organising thoughts before committing them to cassette and paper. And it lent you a crucial second mind, that of someone with secretarial training prepared to say Did You Really Mean That?

When us male executives volunteered for some in-house clinical research for Eric, we had to carry our urine samples past the Pool, while the audiotypists laughed their headphones off. But it proved that a pharmaceutical physician could organise a piss up in a sock factory.

(Having waited 50 years for the chance to write that, for me it's Mission Complete).

References, further information and some good-humoured goodies are at Hugh's special website for PP readers, colleagues, counterparts and acquaintances.

www.just1.org.uk/pphunnybonus

Hugh Gibbons