Medicines for Children

Summary of a Symposium organised by the Academy of Medical Sciences Forum at the Royal Institute of British Architects, London, 14 June 2004

This paper should be read in conjunction with the speakers' abstracts which are attached at Appendix A.

In opening the first session on Requirements and Resources, the Chairman, **Sir Alasdair Breckenridge** (MHRA) summarised the currently unsatisfactory state of the provision of medicines for children: there was usually only limited evidence for efficacy and safety, formulations were often unsuitable and dose selection uncertain. Issues for conducting clinical trials – relating to ethics, recruitment and incentives – would be discussed in detail in the Symposium and these issues concerned academia, industry, regulatory bodies and the public.

Sir Alasdair also delivered a message on behalf of the Health Minister, Lord Warner: Government emphasised that medicines should be appropriately formulated and licensed; that the topic of medicines for children would be a priority for the UK Presidency of the EU in 2005; that new funds were being provided for the expansion of paediatric research networks; and that other necessary actions would be taken while awaiting the EU Regulation on paediatric medicines.

Julia Dunne (MHRA) reviewed the *Regulatory requirements for medicines in children.* There are currently no specific requirements or regulations in the EU. The 1999 ICH guidelines advise that paediatric patients should be given medicines that have been appropriately evaluated and formulated, and drug development plans should include paediatric populations when use in those less than 18 years old is anticipated. However, for those drugs with potential paediatric use approved by the EMEA centralised procedure over the period 1995–2004, only 45% had a paediatric indication at authorisation. Furthermore, unlicensed/ off-label medicines were used for 90% of patients in neonatal Intensive Care Units, 70% in paediatric ICUs, 50% in medical/surgical paediatric wards and 30% in primary care.

The EU is behind the US in relevant legislation, but a draft proposal for a Regulation is now out for public consultation. The Commission hopes to adopt the proposal by mid 2004 and finalise the Regulation by the end of 2006 (hence the priority for the UK Presidency in 2005). The objectives of the Regulation are to increase high quality research into medicines for children, increase the availability of authorised medical products and improve the information available on the use of medicines for children. The proposal contains key elements:

- To establish a new EMEA advisory body, the European Paediatric Board (PB);
- For new products, to require companies to prepare a Paediatric Investigation Plan (PIP), examined and agreed by the PB, whose results will be included in the Marketing authorisation (MA) (and also in applications for new indications, dosage forms and routes of administration);

- For off-patent products, to allow Paediatric Use MA – and this use of the product will be informed by work conducted within a Paediatric Study Programme;
- Incentives for paediatric R&D are proposed – a six-month extension of the existing Supplementary Protection Certificate (SPC), if the MA application contains the results of all measures agreed in the PIP, the product is marketed within 12 months, and relevant information is included in the summary of product characteristics. For older drugs, the proposed incentive is 10 years exclusivity on data within the submission;
- Requiring other industry and regulatory body commitments - to market in all Member States, to conduct effective pharmacovigilance, to develop clinical trial networks and databases at the EU level and an inventory of therapeutic needs to guide finding in the Paediatric Study Programme. This inventory construction will be challenging and the funding and management of the Programme will be controversial.

While this EU Regulation is being progressed, the MHRA is acting to collect relevant information (e.g. from MA holders granted FDA exclusivity), to agree guidance (e.g. on paediatric pharmacovigilance) and to encourage companies in paediatric medicine development. In addition, a major part of the newly established UK Clinical Research Collaboration will be focusing on the NHS Research Networks for Infants and Children.

In opening the discussion, **Charles Bouchard** (MSD, Belgium) presented the perspective from EFPIA on the proposed EU Regulation. The European pharmaceutical sector supported the original European Health Council resolution in 2000 and welcomed its objectives to encourage European paediatric research, build infrastructure and generate appropriate labelling, while avoiding delay in new product approval. EFPIA observed that the US FDA initiative had succeeded very well but expressed concerns on some of the EU recommendations:

i. EFPIA objects to the mandatory requirement to submit PIP results at the time of MA filing, advising that there should be no such linkage between submissions of paediatric and adult data;
ii. EFPIA proposes a 12 month rather than 6 month extension of existing rights, whether SPC or patent, in order to achieve a similar impact to the US incentive, i.e. adjusting for the smaller size of the EU markets and compensating for the delay in building infrastructure and the relative weakness of EU public research (Framework Programmes) by comparison with the US NIH;
iii. EFPIA accepts the obligation to market, subject to national pricing and reimbursement procedures having been concluded.

Subsequent general discussion debated whether the EFPIA request for an extended period of protection could be perceived as excessive or merely designed to render the Regulation effective and the EU competitive with the US. Moreover, the EFPIA recommendation to assess an application in children usually only after evaluation in adults can be seen as an ethical position (minimising harm) but the current situation – unregulated and haphazard – is unsatisfactory and discussants differed on the extent to which it was judged advisable to defer paediatric research, potentially disadvantaging children, until adult studies were completed. Discussants were agreed, however, in

expressing frustration at the slow pace of EU developments and queried whether studies should be initiated now, pending legislation. While there was a precedent – when SPC legislation was first introduced (with a catchment period) – it might be difficult to introduce retrospective incentives, and the new requirement that the Commission must perform Impact Assessment before legislating has added to the general uncertainty. Discussants also emphasised a key scientific point – that the data generated must be specific for age groups rather than assuming that paediatric data are homogenous.

Greg Kearns (Children's Mercy Hospitals and Clinics, Kansas City) described the US experience: *Paediatric trial networks and trial personnel.* In the US, approximately 80% of marketed drugs are not yet suitably labelled for paediatric use so that determining an appropriate dose is a major issue. However, previous challenges and constraints to paediatric R&D (whether scientific, logistical, legal, ethical, programmatic or regulatory) are not now perceived as insurmountable and the FDA initiatives (1997 Paediatric Study Regulations; 2003 Paediatric Final Rule) have been accompanied by the development of new research networks (see abstract). The NIH Paediatric Pharmacology Research Unit (PPRU) Network was described in detail – the initial primary mission was improved paediatric labelling but there has been a growing emphasis on translational science (and now also on basic research). Work is predominantly Phase I and II with some Phase III plus off-patent drug initiatives – this is a network of clinical pharmacology rather than clinical trials.

The essential characteristic of a PPRU is cooperation within the institution and collaboration between institutions and networks (including internationally) – to embody expertise within the specialised, multidisciplinary centre of excellence for patient care, formulation skills, clinical trial design and management, pharmacokinetic and pharmacodynamic (PK/PD) studies and translational science (including pharmacogenetics, bioinformatics, experimental medicine).

One point raised in discussion related to the role of parents in PPRU activities – this role was acknowledged to be very important and the recent report from the Institute of Medicine ("The ethical conduct of clinical research involving children") was cited as providing guidance, e.g. on compensation for parents (subsistence expenses) as well as appropriate incentives for the child. The process for priority setting for the portfolio of activities within a PPRU was also clarified – priorities are determined by the institution, which also has input into the design of externally funded protocols.

Tony Nunn (Royal Liverpool Children's NHS Trust) covered *Formulation of medicines for children* as part of the second session of the Symposium on Technical, Scientific and Medical Issues. There is a history of clinical pharmacology concerns in paediatric medicine relating to excipients as well as the active drug substance, e.g. diethyleneglycol as solubiliser, benzyl alcohol as preservative, sucrose and dental caries, azodyes and hyperactivity. There are also important pharmacy considerations with regard to the adaptation of adult dosage forms and off-label use. Age-dependent changes in the appropriate magnitude of the dose and ability to cope with dosage forms require a range of dosage formulations and routes of administration in paediatric medicine. Particular problems arise for younger children unable to swallow tablets or capsules, although modern dosage forms bring some advantages (even if initially designed for adults, see abstract). Extemporaneous dispensing by pharmacists

introduces several formulation and stability issues associated with quality control of the procedure, validation of shelf life of the product, characterisation of bioavailability, and the absence of standard preparations.

In looking to the future, the desired paediatric formulation can be specified as: minimum dosage and frequency of dosing, one dosage form appropriate for all patients, minimum impact on life style of recipient, non-toxic excipients. In the meantime, it must be recognised, that children require a better choice of dosage forms; while the situation in the EU may improve after 2006, there is need now to persuade manufacturers to provide alternative formulations and to ensure that pharmacists and carers have sufficient information when adapting current dosage forms.

Among the points emerging in discussion:

- Referring to previous presentations, it was reiterated that there are particular problems in off-label use in the neonatal ICU;
- Pharmaceutical technology advances, e.g. in nano-milling, are not within the scope of the pharmacy – might there be a role for manufacturers to prepare new formulations on behalf of the pharmacy?
- Pharmacies with a particular expertise have a broader role and responsibility in acting as a "help desk" to advise others.

Gérard Pons (Saint Vincent de Paul Hospital, Paris) provided an overview on *Drug metabolism and pharmacokinetics in children*, covering drug absorption, distribution, metabolism and excretion (see abstract for details). Different metabolic pathways demonstrate different maturational profiles during development, as exemplified by variability in the cytochrome P450-dependent enzymes. Hence, drugs are metabolised in different ways according to age, e.g. the variation in relative degree of glucuronidation and sulphation of paracetamol.

In summarising across the PK determinants, by comparison with adults, neonates have decreased drug clearance so require lower relative dose to avoid risk of overdose, while infants have increased clearance so require higher relative dose, to avoid risk of sub-therapeutic response. As detailed in the abstract, children must be regarded as a heterogeneous group (ICH classification). As a consequence, PK data obtained in adults cannot be extrapolated to children using a proportionality rule based either upon body weight or surface area.

In discussion, the potential value in constructing a comprehensive database of cytochrome P450 protein maturation was noted, in order to interpret and predict age-dependent changes in drug metabolism and in drug disposition. This prediction may help at focussing more appropriately drug studies during drug development according to age and facilitate the assessment of PK parameters and the dose required according to various age classes. However, equivalent data are not yet collated for different adult (ethnic) groups - and such work would also aid better understanding of genetic influences on the variation in drug metabolising enzymes.

Terence Stephenson (Queen's Medical Centre, Nottingham) considered *How children's responses to drugs differ from adults.* As a broad generalisation it was

judged that, by contrast with PKs, children's PD response to drugs differs less and the adult-child differences that have sometimes been assumed can often be attributed to inadequate data.

However, there are some well-established examples of PD differences:

- Different variants of disease; e.g. genetic epilepsies associated with channelopathies in children show a better response to standard drugs, blocking voltage-gated ion channels;
- Effect of development on ADRs; e.g. increased valproate hepatotoxicity in young children, tetracycline stain of developing enamel, chloramphenicol and grey baby/young infant syndrome (variable conjugation by UDP-glucuronyltransferase isoforms);
- Age-dependent differences in drug effectiveness; e.g. warfarin (at similar blood levels);
- Pharmacogenomics; e.g. receptor polymorphism to Beta-2 bronchodilator agonists, and developmental pharmacogenomics; e.g. gene switching during development or different isoforms from post-translational splicing during development.

There is also the possibility of "programming" – a permanent effect of a stimulus applied at a sensitive point in development; animal research suggests the possibility of such an effect with corticosteroids and this might have implications for post-natal use of steroids.

While many have noted the impediments to paediatric research (e.g. small market size, concerns on litigation, ethical issues), Professor Stephenson contended that there were significant opportunities for new research, illustrated by discussion of the PIVOT (Pneumonia IV versus Oral Treatment) study, the first randomised control trial for children with community acquired infection, and by the enthusiasm for the new UK research network, if the new funding is used wisely.

In discussion, it was agreed that PD differences are more pronounced in neonates. The issue of what needs to be done in research across the EU to match the US research excellence was again raised – and whether development of networks dilutes the focus of public funding on centres of excellence. The preferred position may be a network comprising a relatively small number of centres, each with critical mass.

The third session, Practical Experience with Clinical Trials in Children, focusing on disease area case studies, commenced with **Andrew Pearson** (University of Newcastle upon Tyne) providing an overview on *Clinical trials in childhood cancer*, with particular reference to Phase I, II and III and pharmacological studies. The UK Children's Cancer Study Group (UKCCSG) now provides a national, multidisciplinary approach to advancing care through research, being responsible for both protocol development and trial management, and with strong links to the National Alliance of Childhood Cancer Patient Organisations. There is an established UKCCSG pharmacology network involving 13 centres and European links. Specific objectives and scientific issues are described in the abstract and, reinforcing points made by previous speakers, some of the key practical challenges identified were:

- Lack of appropriate drug formulations – capsules often cannot be taken by young children (e.g. 6-mercaptpurine, temozolomide), suspensions may be unpalatable and disguising taste (e.g. opening 13 *cis* retinoic acid capsules into ice cream) may reduce bioavailability;
- Inappropriately delaying paediatric medicine research and access until after adult clinical development is completed – early effort is recommended in paediatric tumour models in order to identify whether paediatric development might be warranted;
- Dose selection has often been empirical but a dosing strategy should now be based on data relating safety to blood levels – such studies are often constrained by lack of resource, e.g. research nurse availability;
- Clinical trial recruitment – while 80% of eligible patients enter Phase III studies, randomisation rates are still lower than in other European countries; the development of specialised phase I-II centres is also needed.

Discussion concentrated on issues for trial design and management – the objective to demonstrate clinical superiority in new agents (rather than equivalence) requiring relatively large trials. In consequence, international collaborations were essential in recruiting into large trials. The use of population PK and PD measurements was found to be very useful in smaller studies. Professor Pearson also noted that the impact of the European Clinical Trials Directive had not been especially problematic although additional data management resource is now required.

Michael Levin (Imperial College London) described his experience with *Clinical trials in childhood infection* with particular reference to meningococcal sepsis, where mortality rates had, essentially, little improved during the last 50 years. Although there has been significant progress in characterising the role of mediators of inflammation in multiple organ failure, the availability of many potential sites for therapeutic intervention (e.g. endotoxin production, cytokine receptors, clotting pathways) had inspired enthusiastic initial investigations but little controlled clinical trial data on comparative efficacy or safety. For example, it is difficult to interpret the retrospective analysis of high rates of intracranial haemorrhage after use of t-PA because there are no control data.

While there is need for placebo-controlled study of experimental therapies in this indication, such studies are difficult to conduct because of the very rapid progression of sepsis and because patients are often too sick to be moved to a specialised research centre. In this context, the development of a regional centre with specialised resuscitation and transport facilities was found helpful in reducing mortality rates. But there are other problems:

- The meningococcal market may be perceived as too small to support commercial development of therapeutic agents even if there is good initial evidence of improved outcomes, e.g. for Bactericidal Permeability Inducing Protein;
- It can be difficult to evaluate and extrapolate the potential paediatric relevance of data collected in adult studies. For example, in the PROWESS adult meningitis study, correcting a dysfunction in activated protein C decreased mortality but increased bleeding risk – what is the likelihood and what might be the implications of finding a different risk-benefit in children?

In discussion, the reason for decreased mortality in the specialised paediatric research unit was explored further, being attributed to better understanding of pathophysiology and the introduction of standardised algorithms for clinical practice rather than to the availability of new therapies.

The final case study was contributed by **Mike Devoy** (GlaxoSmithKline) on *Clinical trials in young children with asthma*. National Asthma Campaign data show that paediatric asthma episodes reported in the UK (in 2001) are six-fold higher than 25 years earlier. There are many practical issues for research with the youngest children (1-4 years old) who bear the greatest burden of disease (see abstract for details). For example, there may be difficulties in distinguishing wheezing phenotypes in early childhood; there is a need to recruit and measure efficacy of intervention in terms of symptom severity and frequency rather than lung function measurement; sample (urine, blood) collection techniques may need to be customized and cannot be assessed in terms of a laboratory normal range of values; and relatively slow recruitment rates must be envisaged. Safety endpoints in children receiving steroids also need particular attention – and new FDA requirements for steroid growth studies set demanding standards for the duration of measurement, need for comparators, study size and analysis.

Practical lessons learned from the conduct of asthma studies with young children can be generalised – the importance of identifying good research clinics; involving parents (in supporting their child and recording outcomes); increasing General Practitioner referral and involvement; planning to achieve realistic recruitment timeframes and choosing appropriate endpoints. Research management issues were further emphasised in discussion - the need for good planning and realistic goals, the incorporation of research training during the preparative phases rather than during recruitment, together with recognition of the potential value of NHS patient information databases in identifying participants.

The final session on Unmet Needs and Parental Concerns opened with a presentation by **Sir David Hull** (Royal College of Paediatrics and Child Health) characterising the historical interplay of scientific, economic and political issues. In reviewing recent developments across a range of challenges (see abstract), the following points were highlighted:

- Information – the British National Formulary was now taking over the effort to develop a formulary of medicines for children that brought together evidence on best practice (including off-label/unlicensed uses) with protocols. It is hoped that this development will reassure Trusts that unlicensed medicines could be used, while also identifying those medicines that require further inquiry;
- Interpretation – it is agreed that the Commission's proposed Regulation is a worthy objective, if the Paediatric Board has the professional ability to interpret the relevance of data to children at different stages of development and providing that prescribing is not excessively restricted;
- Surveillance and clinical appraisal – much more needs to be done to identify the evidence available to support dose selection. This is proposed as a professional responsibility of the health services such that all practitioners should expect to be involved in structured evaluation rather than relying on the enthusiasm of a few researchers. Randomised control trials may be impractical (e.g. in rare diseases)

and structured observational studies can be very helpful – particularly in recording developmental diversity.

Individual personal perspectives on medicines for children were contributed by three parents:

- **Peter Richards** (experience with epilepsy) emphasised that parents and carers had much to contribute as reliable witnesses of research, based on their long-term experience and consistent observation. Particular concerns were raised relating to potential long-term safety issues; the importance of facilitating delivery mechanisms for emergency medication; and assessing drug efficacy in terms of quality of life improvements.
- **Danielle Taylor** (experience with Acute Lymphoblastic Leukaemia) raised several concerns relating to formulation of medicines (e.g. need to differentiate packaging of different doses) and clinical trial participation: the difficulty of making informed decision to consent, particularly with respect to parental understanding as to whether a randomised clinical trial was addressing an important area of uncertainty. This individual experience identified important general issues for parent-investigator relationship, how much information should be provided when seeking consent and whether there should be more lay involvement in protocol development.
- **Richard Palmer** (Chairman of the National Alliance of Childhood Cancer Parent Organisations and a parent of a child who had cancer) provided further perspective on a range of issues relating to parent's expectations, their attitudes to randomised trials and desire for information prior to participation.

Parents often do not understand the complexities – in science, clinical procedures, regulations – and need simpler information together with good rationale for involving their children in research;
There must be pragmatic, better, use of existing information (so that trials do not unnecessarily duplicate previous work) and strengthening of the scientific interchange, across companies, academia and medical research charities;
Small populations necessitate introduction of new research methodologies;
The availability of new drugs and better treatments must not be limited by raising barriers for entry and there must be appropriate incentives for all involved.

In the final general discussion, many of the points made by parents (and other speakers) were reinforced:

- Parents should be more involved in collecting data;
- Better international sharing of data by researchers might help to prevent trials being initiated unnecessarily. Because it can be difficult to fully inform participants during times of great stress, parents are asked to trust researchers but parents also need to know that research is approved by ethics review and is not duplicating what is already known;
- Randomisation into a research trial at the time of diagnosis is often a difficult challenge for all involved – what are the alternatives? The research design options need to be better debated within the research community – for example can information be collated from separate studies rather than from the randomised arms within a study?

In summary, **Sir Colin Dollery** (Academy of Medical Sciences and GlaxoSmithKline) emphasised some of the principal messages emerging from this Symposium for attaining the objective of safe and effective therapies of appropriate dosage form. While the EU was now following the US model in combining regulation and incentives to address the hitherto unmet medical needs, this will require significant effort to be successful across the heterogeneous European cultures. Key prerequisites can also be identified:

- Medical personnel – particularly leadership in paediatric research combined with expertise in experimental medicine (and advanced technology, e.g. imaging facilities appropriate to children) but also new cohorts, e.g. research nurses, to combine a high standard of care with research excellence;
- Specialist research centres – how many centres will Europe need?
- Parental commitment – and taking account of the issues raised by parents;
- Medicines – while many now advocate initiating early research on new drugs for children, would this be appropriate for agents acting on novel targets when so little is known about safety?
- Formulation – a need for differentiated dosage forms and new regulatory requirements for stability and reproducibility data;
- Informatics capability – to improve collection and use of both "soft" data (e.g. observations from parents) and "hard" data (e.g. maturation of drug metabolising enzymes);
- Funding – a need for Government to set up centres to emulate the US research excellence; for industry to collaborate with the expert academic centres and patient groups; and for patient groups to develop educational and advocacy strategies to influence policy makers.

In conclusion, Sir Colin reiterated that this Symposium was intended to stimulate ongoing dialogue. Reflecting the initial request from the Health Minister, the Academy of Medical Sciences now invites further comment on issues to take forward – particularly in the context of the UK EU Presidency priorities for 2005.

Robin Fears, July 2004

Notes:

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GLOSSARY

MHRA	Medicines and Healthcare Products Regulatory Agency
EMEA	European Medicines Agency
ICU	Intensive care unit
PIP	Paediatric Investigation Plan
SPC	Supplementary Protection Certificate
MA	Marketing Authorisation
EFPIA	European Federation of Pharmaceutical Industries & Associations
FDA	Food and Drug Administration (US)
PB	(European) Paediatric Board
US NIH	US National Institutes of Health
ADR	Adverse drug reaction
ICH	International conference on harmonization
PK/PD	Pharmacokinetics/pharmacodynamics
UKCCSG	United Kingdom's Children's Cancer Study Group

APPENDIX A: ABSTRACTS

Programs and Networks for Paediatric Clinical Pharmacology

Dr Gregory L. Kearns, Pharm.D., Ph.D. (Marion Merrell Dow / Missouri Chair of Pediatric Pharmacology; Professor of Pediatrics and Pharmacology, University of Missouri – Kansas City; Chief, Division of Pediatric Pharmacology and Medical Toxicology, Children's Mercy Hospitals and Clinics, Kansas City, Missouri USA)

The successful study of drug disposition, action, efficacy and safety in paediatric patients requires a carefully orchestrated, multidisciplinary collaboration. An outstanding environment for the delivery of patient care does not necessarily translate into an ideal site for the conduct of a clinical trial. In contrast, the excellent paediatric clinical trial often emanates from an institution where a specialized infrastructure has been assembled.

The framework of an institutional infrastructure for conducting a paediatric clinical trial will be determined, to a great extent, by the nature of a specific clinical trial. Evaluations of drug safety / efficacy (Phase III trials) can be successfully completed by clinicians who provide care for infants and children with a specific condition under study provided that they are supported by clinical research coordinators (eg., nurses, pharmacists) who are specifically skilled in clinical trials. Clinical trials which have pharmacokinetic and/or pharmacodynamics objectives as their primary goal (eg. Phase I – II trials) are best accomplished when a study "team" is assembled consisting of professionals with complimentary expertise (eg., paediatricians, clinical pharmacologists, nurse research coordinators, pharmacists), all skilled in the care / treatment of infants, children and adolescents as well as the rigors of clinical investigation. Finally, the successful conduct of any clinical investigation requires specific institutional resources (eg., a human ethical committee, an office(r) to address regulatory / compliance issues, a research pharmacy, a grants/contracts office) that are dedicated to the research process and serve to facilitate it as well as to protect the institution, the professionals involved in the research process and most importantly, the patients who serve as participants in the research.

In both the United States and Europe, new (and pending) regulations and legislation focused on enhancing the inclusion of paediatric patients as subjects in clinical drug trials has created a demand for increased numbers of Phase I through III studies in this subpopulation. In many instances, this demand exceeds the capacity of a given program or institution to effectively conduct multiple investigations and also, the internal capacity of pharmaceutical companies to create internal pediatric programs *de novo*. In an attempt to address this challenge, pediatric clinical pharmacology networks have evolved in the U.S. (eg., the NIH Pediatric Pharmacology Research Unit Network) and currently, are "under development" in several European countries (eg., the U.K., the Netherlands, France, Germany). To function effectively, these "networks" must be comprised of institutions which have demonstrated capability in the conduct of paediatric clinical trials, both independently and in collaboration with other institutions. As well, they must contain institutions that bring complimentary expertise to the venture, working in a cooperative and collaborative relationship so as to bring a "multiplier effect" to the effort as a whole. Ideally, such networks will have expertise in the requisite areas representing pediatric clinical pharmacology (eg.,

formulation development, bioanalytical, pharmacokinetic/pharmacodynamics analyses, pharmacogenetics/pharmacogenomics) and as a cooperative, be able to leverage involvement with various paediatric subspecialties required to add truly specialized expertise to study design and interpretation, and to provide skilled capabilities for the identification and evaluation of potential study participants.

Formulation of Medicines for Children

Mr Anthony J Nunn (Clinical Director of Pharmacy, Royal Liverpool Children's NHS Trust)

Clinical pharmacology and paediatric medicine usually focus on the drug substance or 'active' and less frequently on the drug preparation and its other ingredients (excipients). However, pure drug substances are rarely administered to patients but are presented as dosage forms suitable for the intended route of administration, for example tablets, capsules and liquids for oral administration. With the addition of excipients, drug substances are turned into suitable preparations by formulation scientists, taking into account acceptability to the patient or carer; the need for physical, chemical and microbial stability to provide an adequate expiry period during distribution, storage and use; interactions with packaging and administration materials and the problems of handling materials on a manufacturing scale.

Many medicines are administered orally to children so taste, texture and smell are very important for acceptability. Because childhood and adolescence span a variety of ages, weights, preferences and abilities, a range of preparations may be required to allow accurate and convenient dose administration to all paediatric age groups. Infants and children may benefit from modern oral dosage forms including sustained release solid and liquid formulations, fast-dissolving solid doses for buccal or oral administration, chewable tablets and multiple unit dosage forms containing solid particles with variable drug release characteristics. Such ranges of preparations may be limited because of commercial constraints but where the market is large the pharmaceutical industry has demonstrated that it can be innovative and meet the needs of the diverse paediatric population. However, many medicines for children are used 'off-label' so the commercial drug preparation has been designed for adults and is often presented as an adult single dose. Administration to the child may require manipulation such as cutting or crushing of tablets, opening of capsules, dispersing in water or addition of powder to food.

If suitable formulations are not commercially available they may be prepared extemporaneously or manufactured on a small scale by pharmacists manipulating various drugs and chemicals using traditional compounding techniques. The practice is widespread and may use commercial dosage forms (e.g. tablets, capsules, injections) as starting materials or pure chemical ingredients. Formulations may be published in national reference works and journals or may have been constructed 'in house'. The physical, chemical and microbiological shelf life of the products may have been established with appropriate tests or may have been assigned arbitrarily. Rarely are bioavailability studies performed to demonstrate that extemporaneous preparations have the same absorption characteristics as commercial preparations.

The availability of licensed formulations of medicines specifically designed for children is far from optimal. Improvements in licensing regulations may provide the

incentives to produce a variety of modern dosage forms that help improve compliance and concordance and exert minimum effect on life style. Until this happens it is important that carers and pharmacists have sufficient information to adapt 'adult' dosage forms to the needs of children.

Drug metabolism and pharmacokinetics in Children

Professor Gerard Pons, MD, PhD (Paediatric and Perinatal Pharmacology –
Rene Descartes University – Saint Vincent de Paul Hospital, Paris, France)

Children are different because they cannot take their medications like adults. They cannot swallow tablets or capsules below 6 years of age. They therefore need specific drug formulations: solutions, suspensions, powder, microgranules. The formulations have to have a good acceptability, i.e good palatability. IV formulations need to have appropriate concentrations: aliquots of sufficient volume have to be handle for adequate precision and safety. Intramuscular injections are painful and sometimes at risk of side effects. Aerosol sprays for asthmatic children cannot be used reliably below 8 years and children need to use a special device, an inhalation chamber.

Children are different from adults because drugs behave differently in their body. The fate of drugs is different in the body of children. The effect of drugs is different in children: the magnitude of the response may be different; the nature of the response may be different, some side effects only occur in children as their bodies undergo growth and maturation.

Data regarding the influence of maturation on intestinal **drug absorption** are scanty probably due to the invasiveness of availability studies. Rectal route is a very interesting route for rapid and large absorption of diazepam in the treatment of convulsions in emergency situations. Cutaneous absorption is a matter of concern in children as the relatively higher dose absorbed through the skin compared to adults is likely to be associated with systemic side effects.

Most of the maturational changes regarding **drug distribution** occur during the first year of life. Drug distribution in body water is characterised by increased volumes of distribution mostly during the first year of life. The differences regarding the distribution in body fat is mostly observed in infants. Protein binding to albumin and α1-glycoprotein is decreased in neonates and the maturation reaches the adult level before the end of the first year of life.

As a whole the expected differences compared to adults are characterised by higher volumes of distribution during the first year of life.

Maturational changes in **drug metabolism** in children are defined by two main features: the different maturational profiles of the various metabolic pathways, the maturity being consequently reached at different ages of childhood; the second main feature is the higher metabolic clearance in infants and young children as compared to adults.

Most of the maturational changes in **drug elimination** through glomerular filtration and elimination occurs during the first month of life.

These various maturational pharmacokinetic changes in children illustrate that roughly the clearances of drugs in neonates are decreased and neonates need lower doses. Otherwise they are at risk of overdose. On the other hand infants drug clearances are increased. Consequently infants require doses higher than adults. Otherwise they are at risk of receiving subtherapeutic doses.
Not only are children different but they represent an heterogeneous group in which different age classes had to be distinguished because they differ regarding drug fate and also drug effect. The international consensus obtained during the International Conference of Harmonisation (ICH E-11) separated four age classes in children: neonates between 0-28 days, infants 29 days – 23 months, children 2 years-11 years and adolescents between 12 and 16/18 years). These age classes are important and should be taken into account both in the planning of clinical studies in children, particularly pharmacokinetics studies, and in drug dosage recommendations at the time of labelling.
Because children are different compared to adults, data obtained in adults cannot simply be extrapolated to children using a proportionality rule based upon body size (weight or body surface area).

Prediction of doses for Children
Dr Karin Jorga (Global Head Modeling and Simulation, Clinical Pharmacology, F. Hoffmann-La Roche, Switzerland) (Unable to attend the meeting).

It is well recognized that children are not just small adults and well-conducted pharmacokinetic and pharmacodynamic studies are needed to determine the appropriate doses for newborns, infants, children and adolescents. Numerous physiological processes change throughout the development from childhood to adulthood and simple dose adjustments by body size are not likely to be appropriate for the majority of drugs.
Most of the drugs on the market are originally developed for adults and dose selection is based on an optimal balance between clinical efficacy and safety. For those compounds, where it is assumed that the pharmacological action in adults and children is similar (e.g. antivirals and antibiotics) an appropriate pediatric dose would be one that gives similar exposures (blood drug levels) to those observed in adults at the recommended therapeutic dose. Without any prior knowledge on the pharmacokinetic characteristics of the drug, the intuitive approach is to administer smaller doses to children. Usually the adult dose is taken as guidance and the dose scaled down depending either on body weight or body surface area. For some compounds such as for example saquinavir - a protease inhibitor for the treatment of HIV - this can lead to substantial underexposure in children as they metabolize the compound much faster. For other drugs body area scaling works well for a certain range of children, but it usually fails in newborns and adolescents, where many different processes change at the same time and absorption, distribution, metabolism and excretion transform quickly and vary widely. One attempt to optimize the dose predictions in children is the application of physiologically-based pharmacokinetic (PBPK) modeling. For every age group models are developed that include the information on organ weights, blood flows and metabolic capacity characteristic for certain stages of maturation. At the moment the experience with these models is still limited as validated information on the physiological parameters is sparse.

Nevertheless, it is expected that such models will develop further in the future and allow a better integration of the underlying processes and improve the predictions of doses in children.
In conclusion, predicting doses for children is complex as numerous physiological processes change and vary during infancy and childhood. A thorough understanding of the pharmacokinetics and pharmacodynamics of the compound is needed to dose adequately in children. Currently, clinicians are required to use medicines with incomplete knowledge about their pharmacological properties and the simple approach to adjust dose by body size bears substantial risks. Further clinical studies are needed to improve our understanding of the behavior of drugs in children and provide better guidance on dose.

Clinical Trials in Childhood Cancer
Professor Andrew DJ Pearson (Professor of Paediatric Oncology, University of Newcastle upon Tyne; Chairman of the United Kingdom Children's Cancer Study Group)

Each year 1,200 children in the United Kingdom under the age of 15 years develop a malignancy. The survival of children with cancer has progressively increased over the last three decades, so that currently the five-year survival rate is 75%. In view of the frequency of childhood cancer it is essential that trials be carried out on a national basis and in most cases an international. Furthermore it is vital that all the maximum number of eligible patients are entered into these trials.

In 1977 the United Kingdom Children's Cancer Study Group (UKCCSG) was formed. This group is a national multi-disciplinary, organisation, which aims to advance the care of children with cancer through clinical research. The ultimate objective of the Group is to improve the outcome of children with poor prognosis malignancy and maintain excellent rates of cure, while reducing long-term toxicity, for those with good prognosis disease. The UKCCSG has a network of nearly 500 members from 22 United Kingdom treatment centres. Its hub is the UKCCSG Data Centre in Leicester, which is responsible for administration of the research studies and from where all the activities of the group are co-ordinated. The trial portfolio of UKCCSG includes 36 phase I, II and III, pharmacological and late-effects trials and 30 biological studies. A parallel organisation, the United Kingdoms Childhood Leukaemia Working party (UKCLWP), is responsible for trials in children with leukaemia.

A central objective for Phase III trials is to open randomised international studies for most tumour types. Fourteen of the most recent 18 phase III trials opened were international. For example, for neuroblastoma 16 European countries have joined together to form SIOP Europe Neuroblastoma Group and the current high risk study recruits 240 patients per year and investigates three randomised hypotheses. For hepatoblastoma the SIOPEL studies recruit patients from 50 countries and have resulted in dramatic improvements in survival. Currently, the UKCCSG is integrated with European groups and is planning to ensure that its activity complements that of North American.

Phase I /II studies have progressively been developed over the last 17 years, since the creation of the New Agents Group of the UKCCSG in 1987. Between 1987 and

1996 only phase II studies were undertaken, in 1996 the methodology for multi-centre phase I studies was established and currently there are 11 Phase I centres. In 1992, to facilitate recruitment, a French/UK collaboration was established and now the majority of phase I/ II studies are joint initiatives. Further European collaboration, including the Netherlands, Italy and parts of Germany has recently allowed a larger group to be established. A comprehensive programme of drug discovery - the Innovative Therapies for Children with Cancer (ITCC) - has been developed. This programme identifies new agents both from pharmaceutical companies and academic programmes and includes a drug development programme focussing on paediatric targets.

The UKCCSG has an established paediatric oncology/pharmacology group. Currently, 13 geographically separate centres are participating in studies. Pharmacological studies of new anti-cancer agents and established agents have been carried out. Particular themes are the evaluation of the pharmacology and appropriate dosing of anti-cancer agents in infants under the age of one, and high dose chemotherapy. European collaborations have also been established.

This success in clinical trials is now being challenged by three difficulties: - lack of data manager and research nurse infrastructure at the UKCCSG centres especially in view of the recent EU directive for clinical trials; a relatively low rate of randomisation in the United Kingdom, in contrast to other European countries and lack of access to new drugs.

Improving access to new drugs and evaluation in the paediatric population is a crucial issue for children with cancer. Currently, children with malignancy do not have access to a number of new anti-cancer compounds until relatively late in the agent's development, often only when the compounds are commercially available. This reluctance of pharmaceutical companies is particularly problematical. The optimum strategy would be that companies raise the issue of children for each compound entering a clinical development procedure in adults. This would enable preclinical evaluation of the compound's potential anti-tumour activities to be started in appropriate paediatric tumour models in order to identify whether or not the it needs paediatric development. Then, when indicated and appropriate, a paediatric programme would be initiated, as soon as sufficient data is available to ensure safety.

In addition there are challenges facing the availability of established medicines for children with malignancy including difficulties providing the appropriate formulation for existing agents and reluctance to develop a formulation of new agent, for example syrup, specifically for children.

In summary although there has been substantial progress in clinical trials of children with malignancy, significant challenges remain.

Clinical Trials in Young Children with Asthma

Dr Mike Devoy (Vice President of Respiratory Medicine, GlaxoSmithKline, Greenford, UK)

Asthma is the most common chronic disease of childhood and its prevalence continues to increase in most countries of the world. Up to 40 percent of infants are reported to have evidence of wheeze in the first three years of life. Only 10 percent have persistent wheeze that develops into asthma in later childhood. The ability to differentiate between the numerous phenotypes is a fundamental step towards prescribing the most appropriate asthma therapy. Recent studies using novel outcome measures, such as airway resistance (sRAW) and impulse oscillometry, have produced data that can help determine a child's phenotype and relative risk of developing asthma.

Inhaled corticosteroids are considered the most effective anti-inflammatory treatment for all severities of persistent asthma in both adults and children.
Efficacy outcome measures in infants are routinely based upon frequency and severity of symptoms due to the difficulties young children have performing forced lung function techniques. Researchers are dependent upon parents/caregivers to observe and report such symptoms. Recruitment of infants to clinical trials is particularly challenging since successful participation of a child in the trial is not just dependent upon the child's eligibility and cooperation but also the parent in terms of consent, availability to bring the child to clinic and, commitment to comply with the data collection.

Although inhaled corticosteroids are firmly established in the management of asthma, concerns remain as to the possible long-term adverse effects. Growth is a particular issue requiring long-term studies to determine the absolute effect on growth rate and final height.

The conduct of clinical studies to establish the risk-benefit of asthma therapy requires particular attention to strictly define the patient population, keep clinic visits to a minimum whilst collecting data at a level of detail and for an amount of time appropriate for your chosen clinical endpoint.

Unmet needs for drugs in children
Sir David Hull (Past president, Royal College of Paediatrics and Child Health)

Ensuring that children are given effective and safe medicines might be thought to be a central responsibility for any national health service; an overriding duty for those who dispense, prescribe and administer medicines; and a fruitful area for scholarly endeavour. It has been none of these. The development of medicinal treatments is subject to many constraints – scientific, economic, social and political. These are even more daunting when children are involved and as a result, in recent years, children have lost out. That cannot be right or good. Many of the medicines given to children are either unlicensed or given 'off-label'. Problems related to this usage emerged in the early 1990's. To address these it seems important that:

- What is know is more generally known (**Information**),
- What is being given is monitored, particular the use of unlicensed and off label medicines (**Surveillance**),
- Evidence is collated on the significance of what is known about a medicine, to its use in children (**Interpretation**),

- Commitment is given to the clinical appraisal of medicines given to children (**Clinical appraisal**), and
- Medical sciences exploring the action of drugs against the background of development from birth to adolescence are promoted (**Children – developmental biology**).

A start has been made to address all these, e.g. – formulary 'Medicines for Children', - proposed EC legislation 'Better Medicines for Children', - developments described in the RCPCH report 'Safer and Better Medicines for Children'. Progress will depend on how the rules which govern the controlling Authorities are applied, the appraisal of the treatments in the Health Service provision, the attitudes and discipline of the professions involved, as well as the energy of enquiring scientists.

APPENDIX B: PROGRAMME

Symposium on Medicines for Children
Monday 14 June 2004, The Royal Institute of British Architects, 66 Portland Place, London W1

There is widespread concern about the limited evidence available for both efficacy and safety of many medicines used in children. Evidence is often limited to small-scale clinical trials and in some cases is almost non-existent. The reasons are complex. Children only rarely develop serious illnesses. This makes recruitment for clinical trials difficult and provides little incentive for manufacturers to develop special formulations of their products. Many of the medicines prescribed for children are generics so there is little commercial incentive. When children do fall ill doctors often have to prescribe adult formulations that may be unsuitable and doses that have not been validated in that age group. While there are no simple solutions there is a consensus that the situation must be improved. This symposium brings together leading experts from academia, the health service, industry and regulatory bodies to review the current situation and to discus ways and means of bringing about improvements.

Session 1	**Requirements and Resources**
Chairman	Professor Sir Alasdair Breckenridge CBE FRSE FMedSci, Chairman of the Medicines and Healthcare products Regulatory Agency (MHRA).
09.45	**Regulatory requirements for medicines for children** Dr Julia Dunne, MHRA, London UK
	Discussion opened by Dr Charles Bouchard, MSD European Government Affairs
10.15	**Paediatric trial networks and trial personnel** Dr Greg Kearns, Kansas Mercy Childrens' Hospital (USA).
10.45	Coffee
Session II	Technical, scientific and medical issues
Chairman	Professor Patrick Vallance FMedSci, Head of the Division of Medicine, University College London
11.10	**Formulation of medicines for children** Dr Tony Nunn, Director of Clinical Pharmacy, Royal Liverpool Childrens NHS Trust.
11.40	**Drug metabolism and pharmacokinetics in children** Professor Gérard Pons, Groupe Hospitalier Saint Vincent de Paul, Paris

12.10 **Prediction of doses for children**
Dr Karin Jorga, Hoffman La Roche, Basel

12.40 **How children's responses to drugs differ from adults**
Professor Terence Stephenson, Queen's Medical Centre, Nottingham

13.10 Lunch

Session III **Practical experience with clinical trials in children**

Chairman Professor Sir Colin Dollery FMedSci, Senior Officer Academy of Medical Sciences & Senior Consultant, GlaxoSmithKline

14.10 Clinical trials in childhood cancer
Professor Andrew Pearson, University of Newcastle

14.40 **Clinical trials in childhood infections**
Professor Michael Levin, FMedSci, Department of Paediatrics, Imperial College London

15.10 **Clinical trials in young children with asthma**
Dr Mike Devoy respiratory group GlaxoSmithKline

15.40 Tea

Session IV Unmet needs and parental concerns

Chairman Professor Sir Michael Rawlins FMedSci, Chairman of the National Institute for Clinical Excellence

16.05 **Unmet needs for drugs in children**
Sir David Hull, former President of the Royal College of Paediatrics

16.35 **Parental concerns: a personal account**

17.05 **General discussion and summary**

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