JFPM
Edition 3
Oct 18

the JOURNAL of the Faculty of Pharmaceutical Medicine

Paediatric medicines development

Faculty of Pharmaceutical Medicine
Advancing the science and practice of pharmaceutical medicine for the benefit of the public

Journal of the Faculty of Pharmaceutical Medicine

Edition 3
October 2018

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Welcome to the ***Journal of the Faculty of Pharmaceutical Medicine***.

The JFPM is a biannual publication covering all aspects of pharmaceutical medicine and providing updates from all areas of the FPM, and news and events. Each edition will have a main theme, with contributions from FPM members, staff and external guest authors.

This edition focuses on the development and regulation of medicines for children. We have contributions from members of both the FPM and the Royal College of Paediatrics and Child Health. Articles cover Brexit, orphan diseases, PIPs and more. We are also very pleased to present a video interview in which Professor Tim Higenbottam discusses his aims and ambitions for the FPM, in advance of him assuming the Presidency on the 1st November.

Dr Mayur Joshi
Dr Uttara Kurup
JFPM Editors

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1st November
AGM

1st November
Awards Ceremony

1st November
Annual Dinner

2nd November
FPM Annual Symposium

13th November
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22nd November
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WELCOME

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PROFESSOR ANNE GREENOUGH
VICE-PRESIDENT (SCIENCE AND RESEARCH)
RCPCH

Welcome to the third edition of the Journal of the Faculty of Pharmaceutical Medicine which, as you will see, is largely devoted to the development of medicines in paediatrics. When I became President of the FPM, one of my main aims was to develop much closer relationships with other Royal Medical Colleges and Faculties and one of the early links that we established was with the Royal College of Paediatrics and Child Health (RCPCH).

The development of medicines for children has until recently been a bit of a 'Cinderella' subject and it is really only in the last ten years or so that companies and the regulators have started to pay attention to this matter, driven in part by the introduction of the Paediatric Regulations from the EMA and updated regulations by the FDA. Since this change in the regulations much more emphasis has been given to the development of medicines for children with the number of specific development programmes and clinical studies increasing significantly. This has also been influenced by the number of programmes that are targeted towards rare and orphan diseases, which of course are more prevalent in the younger population and are now subject to treatment opportunities.

In this issue you will see that the topic of the development of medicines for children in the EU and the UK is covered together with how this might be affected by Brexit. There is also an article on the development of a gene-based therapy for a rare genetic disorder, which demonstrates the barriers and challenges in working with very young children in clinical studies to treat an inherited genetic based disease. Other articles touch on the key clinical issues in relation to Paediatric Investigation Plans and the role of the NIHR in the UK and the Paediatric Clinical Trials Network which was set up a few years ago.

Through our collaborative working with the FPM, the RCPCH has emphasised that the development of medicines for children and young people is extremely important. We are pleased that they have been able to work with the FPM to discuss these important issues so that the clinical aspects of children's diseases can influence the development of the medicines.

The RCPCH hope that the collaboration will continue and this publication is the first step in bringing this important matter to the attention of everyone involved in medicines development for children.

We hope you enjoy reading this edition.

The development of medicines for children has until recently been a bit of a 'Cinderella' subject and it is really only in the last ten years or so that companies and the regulators have started to pay attention to this matter.

MEDICINES DEVELOPMENT IN CHILDREN: PRINCIPLES APPLIED TO GENE THERAPY FOR A RA

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Drug development is a complex, time-consuming, and rapidly evolving discipline. This is particularly true for gene therapies, which have the potential to dramatically alter the lives of patients and their families, but for which little precedent exists. Furthermore, many severe, rare, genetic diseases are diagnosed in infancy or the first years of life, and working with children adds additional medical, ethical, regulatory, and operational complexities to the study of novel therapeutics.

This article examines the ways in which the general principles of medicines development in children differ from those principles applied to adults, particularly within the context of gene therapy development for rare and fatal congenital diseases. It specifically assesses a systemic adeno-associated virus serotype 8 (AAV8) for X-linked Myotubular Myopathy (XLMTM), currently being developed by Audentes Therapeutics. Consideration is given to the practical and ethical aspects of studying medicines in children in this highly innovative and evolving field, where, with no currently approved alternative therapies, the opportunity to transform the lives and well-being of children and their families is apparent.

X-Linked Myotubular Myopathy: an ideal target for gene therapy

XLMTM is a severe, rare centronuclear myopathy caused by pathogenic variants in the MTM1 gene, which result in a lack or dysfunction of the protein myotubularin. Infants present with severe hypotonia, weakness, and respiratory distress, and nearly half die of respiratory failure in the first year of life. Children who survive infancy require extensive supportive care. Most never achieve independent ambulation, require respiratory support, and die prematurely.

Currently, there are no approved disease-modifying treatments for XLMTM. Clinical management focuses on maximising functional abilities and minimising medical complications through multidisciplinary supportive care[1]. Early work, however, indicates that delivering a functional copy of the MTM1 gene using an AAV8 vector ameliorates symptoms of the disease in animal models[2,3,4], and clinical trials are ongoing with promising early results[5].

Appreciating the differences between children and adults

Children are not small adults. They differ physiologically, which may affect a drug's pharmacokinetics and pharmacodynamics. For example, studies on hepatic drug metabolism show that a person's enzyme activity changes over his or her lifetime, which affects how drugs are metabolised. Physiological differences may also affect a drug's safety profile. For example, the heart rate of a new-born baby is normally approximately 120–140 beats per minute (bpm) and decreases to approximately 70 bpm in adulthood. Therefore, if a drug has a known effect on cardiac parameters such as heart rate, the difference between new-born and adult heart rate bpm should be taken into consideration. Similarly, if a drug is renally excreted, differing glomerular filtration rates between children and adults may produce considerably different safety and toxicity profiles. Inadequate consideration of physiological differences can expose children to a direct risk of under or overdosing and a delayed risk of long-term adverse effects.

In the field of AAV gene therapy, an adverse effect that may be seen in some patients is elevation of liver function tests (LFTs) several weeks after dosing, reflecting a T-cell-mediated inflammatory reaction of hepatocytes. Normal ranges for children's LFTs differ from those seen in adults. Therefore, to accurately assess the degree and clinical relevance of such elevations and implement appropriate medical management, a full understanding of appropriate LFT values across the paediatric age range is necessary.

Understanding the natural history of disease

When developing new therapies, understanding the natural history of the disease is extremely important. Heterogeneity within the same disease may exist between children and adults, and this is an important factor to consider to better understand a disease's natural history. For example, certain types of epileptic seizures, such as Benign Rolandic Epilepsy or Petit Mal epilepsy (absence seizures), or malignancies, such as acute lympohoblastic leukaemia, Wilms tumour and certain central nervous system (CNS) tumours, occur in children more frequently than adults. Other diseases that are common in adulthood, such as ischaemic heart disease or essential hypertension, are extremely rare in children.

ARE AND FATAL PAEDIATRIC DISEASE

Another challenge in understanding the natural history of a rare disease is that there is frequently a lack of published information in the literature for rare diseases [6]. Identifying rare disease experts can also be difficult. Often specialists are few and far between, and many of them have only cared for a small number of children among a specific rare disease population. These factors have an impact on how we design, set up, and operationalise clinical trials.

In the Audentes XLMTM clinical programme, the RECENSUS study was conducted to help us form a deep understanding of the natural history of XLMTM. The study confirmed the high level of mortality and morbidity for XLMTM that had been discussed in the literature, highlighting that 90% of patients required respiratory support at birth, and approximately 50% of patients died within the first 18 months of life[1]. Further, RECENSUS added new findings regarding the considerable disease burden and degree of health care utilisation among these children. In their first year of life, patients underwent an average of 3.7 surgeries and spent 35% of their time in the hospital[1]. Following RECENSUS, we initiated INCEPTUS, a prospective natural history run-in study. These natural history studies provide important comparator data for our subsequent ongoing Phase 1/2 study, ASPIRO.

The marrying of a retrospective chart review and a prospective natural history study with an interventional trial enable us to demonstrate efficacy and safety in a small patient population. For example, we will be able to compare the retrospective chart review data in RECENSUS to the results of the ASPIRO interventional study, and also plan to use the INCEPTUS study as a longitudinal within patient control for the ASPIRO study participants.

The impact of developmental progression

It is important to appreciate the developmental difference between children and adults. Children are growing physically with respect to weight and height, while their organs are maturing in size and capability. Cognitive functioning, social skills, and neurological development are also progressing, and they are maturing in terms of reproductive physiology. Caution must be applied to ensure a medicine given to a child does not affect aspects of their development.

The photo shows Suyash at a patient meeting, spending time with a young boy with XLMTM. As you can see, the boy is profoundly hypotonic and needs ventilatory support due to respiratory muscle insufficiency.

To investigate the potential ways a drug may impact children's development, preclinical studies in immature animals should be included as part of the clinical program. Our XLMTM gene therapy programme explored dose selection, pharmacology, and toxicology in juvenile animal models to assess toxicity, growth, organ maturation, reproductive development, and neuro-behavioural development as these animals matured through adolescence into adulthood.

A topical issue in the field is whether a gene therapy's effect gets 'diluted' as the target organ increases in size. However, in a pre-clinical dog model, our investigational gene therapy for the treatment of XLMTM demonstrated dose dependent improvements, including protein expression levels, muscle and respiratory function, and survival, and the results have proven to be durable. In the study, dogs were dosed at eight weeks of age when the dogs weighed approximately 5 kg. Six years later they weighed 27–28 kg and have maintained an excellent response to their single dose of therapy consistently through this period[2,3,4].

In addition to pre-clinical work, there are numerous requirements to ensure an appropriate safety evaluation of the effects of medications on the development of children and adolescents in clinical trials. Short-term clinical trials, however, cannot determine the effects on their development, for which longer-term studies are needed. The ASPIRO interventional trial will monitor patients for five years, after which the intent is to continue to monitor the children in a long-term safety study or a registry. Importantly for a gene therapy, this would also inform durability of efficacy and understanding of long-term safety. These extension studies allow further exploration of developmental parameters such as growth and pubertal status and are increasingly expected by regulators.

Addressing family matters, and social and emotional development needs

In addition to growing physically, it is important to appreciate that children progress in terms of social and emotional development. Specifically, they develop autonomy and adapt to functioning within society. Information about treatment plans, including the risks and benefits of treatments, should be conveyed to children and their parents or guardians in an appropriate manner. Communication between children and clinicians should be meaningful (i.e. age appropriate and empathetic) when treatments are explained or feedback is solicited. Notably, ethics committees are increasingly sensitive to ensuring that appropriate communication is addressed in clinical trial materials.

Children and families affected by XLMTM are our partners, collaborators, and teachers. We believe that their perspectives should be considered throughout the drug development process, from initiation of a clinical program to its completion and beyond. We accomplish this through activities such as patient focus groups, attendance at patient advocacy meetings, and one-on-one meetings with patient advocacy leaders.

Importantly, our conversations with the XLMTM patient groups had a direct impact on the clinical trial designs. For example, based on conversations with parents and caregivers, we learned that respiratory aspects of the disease are the most worrisome to them. As a result, we elevated the importance of respiratory outcomes measures in our ASPIRO study. Additionally, we added assessments for a variety of functional measures, including, for example, the ability of a child to vocalise and generate sound, as we heard from families that the ability to communicate would be an exceptionally important skill to attain. Ventilators prevent patients with XLMTM from being able to speak, and from a social and emotional perspective, families want to connect with their loved ones affected by XLMTM through speech. In short, we strive to weave the patient and family perspectives into all aspects of the programme.

Understanding the child-focused health care professional

Those who work closely with treating clinicians, investigators, and key opinion leaders (KOLs) appreciate the importance of understanding the motivations and drivers of these groups. Health care professionals (HCPs) working with children must possess a few unique attributes. To be successful, paediatricians and child-focussed HCPs need to be adept communicators, leveraging an age-appropriate communication style. They should embody kind, gentle, and empathetic qualities, demonstrating a high degree of emotional intelligence and sensitivity. Additionally, they should appreciate a holistic approach to caring for patients while taking children's behaviours and feelings into close consideration.

The balance of benefits and risks

It is critical to evaluate the potential benefits and acceptable risks of a drug or therapy before development. Every treatment is associated with both of these factors: the key issue is to what degree one outweighs the other. Such deliberations take on greater complexity when children are being considered for inclusion and treatment in a clinical trial. It is particularly important to consider children's rights, experiences, and well-being as well as parental expectations of HCPs, and the 'emotional urgency' that tends to exist when working with young children.

Before initiating a clinical programme, it is important to consider the unmet medical need. For XLMTM, the unmet need is clear: there is no available treatment and mortality is high. Regulators usually take these factors into consideration when assessing potential therapies for diseases, and they are often willing to expedite discussions that may facilitate an earlier assessment under these conditions. The XLMTM gene therapy program has received both PRIME (Priority Medicines Review) designation in Europe, and RMAT (Regenerative Medicine Advanced Therapy) designation in the United States. These designations demonstrate that regulators recognise the unmet need of XLMTM, appreciate the promising early clinical data, and are willing to collaborate closely to rapidly advance the program toward global regulatory approvals.

Preliminary data from the AAV8 gene therapy study for XLMTM

In August 2018, we reported promising interim safety, efficacy, and muscle biopsy data at the 24-week timepoint from the first dose cohort of ASPIRO.

Data from the first dose cohort demonstrate significant improvements in neuromuscular function as assessed by the CHOP-INTEND scale and increased respiratory function as demonstrated by gains in maximal inspiratory pressure (MIP), a measure of respiratory muscle strength. Perhaps most importantly, we have seen dramatic reductions in ventilator dependence with two of six patients coming off the ventilator completely – something that is nearly unheard of in children with a congenital myopathy who have been ventilated from birth. In addition to these functional outcome measures, muscle biopsy results from the first three patients treated in the study at the six-month timepoint demonstrate highly efficient tissue transduction as indicated by vector copy number, robust myotubularin protein expression as assessed by western blot, and significant improvement in histology as assessed by an independent panel of histopathologists who are reading and interpreting the samples in a blinded manner.

AT132 has been generally well tolerated in patients to date. The few events we have seen have all been without clinical sequelae and manageable with treatment. The ASPIRO study is ongoing.

Concluding remarks

The area of paediatric medicines development continues to evolve, particularly as society increases its focus on children's rights. The United Nations' Convention on the Rights of the Child (UNCRC) is a treaty that contains four core principles including, non-discrimination; devotion to the best interests of the child; the right to life, survival and development; and respect for the views of the child. Those of us involved in paediatric health, including those working on drug development programs that focus on children, have a responsibility to help carry out this treaty. To accomplish this, I advocate for pharmaceutical and biotech companies to build competencies in paediatric medicine, either by setting up a paediatric department, establishing an internal or external cross-functional expert group, or employing appropriate consultants.

Importantly, physicians within the industry need to ensure that that the perspectives of the patient and the family are considered in medical decision-making. Nowhere is this more important than in innovative and rapidly evolving environments that have the potential to make a long-term transformational change, such as gene therapy.

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DEVELOPING MEDICINES FOR CH
POST-BREXIT FUTURE

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Introduction

The withdrawal of the United Kingdom from the European Union (EU) on 29th March 2019 brings significant implications for the clinical development of medicines used by babies, children and young people. At the time of writing (September 4th 2018), the situation is unclear so this contribution reflects a personal view of ways to address these opportunities and challenges. Children are 20% of the UK population and have specific, well-recognised needs for appropriate medicines that bring significant benefits to public health and the economy.

The EU framework for clinical development supports appropriate development of medicines for babies, children and young people

The multiple steps of paediatric medicines development are summarised in Table 1 with an assessment of the current state of play and future plans. Membership of the EU provides a framework for addressing all these steps. While implementation of the framework can be improved, there is a broad consensus that the mechanisms deployed by the European Medicines Agency (EMA), through the Paediatric Regulation, can promote the development of medicines that have benefit for babies, children and young people[1]. Outside the EU, a number of risks may arise that need mitigation. A change in the legal framework may allow some aspirations to be met.

The post-Brexit future should be informed by shared principles

Irrespective of the legal and regulatory framework, important principles are:
1) Medicines, and their development, need to take account of the context in which they are used. For children, this includes maximising the acceptability of medicines when their recipients cannot rationalise taking medicines, minimising the burdens on families, and minimising the burdens that arise from research participation. The UK is relatively strong in implementing this principle.
2) Quality of medicines and predictability of supply is a key influence on the extent to which medicines achieve their goal in paediatrics. Adherence to a treatment plan requires well-planned systems and changes to formulations can cause multiple problems. Even before Brexit, families report significant difficulties maintaining supplies of many medicines that are specific to paediatrics.
3) Clinical development is a global enterprise: the UK cannot go it alone in any aspect of clinical development
4) Regulatory harmonisation is increasingly important. This includes implementation of paediatric standards such as ICH E11 and contributing to the revisions and extensions of these documents[2].

The UK has a number of strengths in paediatric clinical development

From a paediatric perspective, UK strengths include:
1) Infrastructure. In England, National Institute for Health Research Clinical Research Network (NIHR CRN) is the world's leading national health research infrastructure including sites, coordination and Clinical Research Facilities
2) Paediatric patient and public involvement and engagement (PPIE) is extensive, through Young People's Advisory Groups and Generation R[3], and is a model for other countries
3) The MHRA has strength in depth and has been a very strong force for good in paediatric clinical development over many years
4) Formulation science is vibrant in the UK, particularly in paediatrics

HILDREN IN A

The UK environment also supports clinical development through opportunities such as the NHS potential for connected data (e.g. the National Neonatal Research Database[4]) and the 100,000 genomes[5] project and associated investment. Industry has undoubted talent and energy. The integrated approach to ethical reviews and MHRA review is thoroughly embedded in the UK: many other countries will have difficulty meeting the similar requirements of the Clinical Trials Regulation when it is implemented.

Anecdotally, colleagues in industry and academia report that these advantages of the UK do not deliver their full potential. There is some inconsistency, for example, in the delivery of studies through NIHR and in the ethical review of paediatric studies[6]. UK weaknesses include a relative lack of paediatric pharmacometric expertise (compared to Netherlands, Canada, USA, France and Germany). The small number of experienced paediatric pharmacometricians may limit planning and review of clinical development in the UK, particularly with the growing use of modeling and simulation, and extrapolation. MHRA has undertaken a high proportion of reviews for the EMA, in all populations[7]. This capacity needs to be maintained – taking account of the EMA's free advice about paediatric medicines development.

Uncertainties contribute to difficulties in developing policy and practice

The market size for the UK (12 million people aged 0 – 14 years) is markedly smaller than for the EU27 (73 million people aged 0 – 14 years). This will affect decisions to place studies in the UK, or even to market medicines in the UK. Modifications to legal, regulatory or policy frameworks may mitigate or exacerbate the impact of leaving the EU. UK-specific initiatives in pharmaceutical policy that push or pull clinical development may be possible but need to be integrated with domestic concerns (such as the relationship between value for money and rapid access to new therapies) and to be compatible with initiatives in other markets. Europe is particularly rich in collaboration for pre-clinical and clinical development of paediatric medicines. Including rare diseases, there are five paediatric research infrastructures under development. UK contributes to all of these, including leadership roles.

This work provides an opportunity to influence and to maintain compatibility with Europe, but is at risk from uncertainties relating to research funding and regulatory practice.

Implications

Development of medicines for babies, children and young people could get worse, stay the same, or improve. "Staying the same" is likely to involve new costs relating to tariff and non-tariff barriers to trade and research. The most likely outcome is a mixture so that some things get worse, some stay the same, and others improve.

In order to make the most of the situation we need a continued awareness of the importance of medicines that are appropriate to babies, children and young people and an awareness that appropriate research is essential.

The risks of losing ground and inconsistent adjustment to the post-Brexit future can be addressed through communication and integrated effort in the UK. This should involve emphasis on excellent delivery in the NIHR CRN[8] (and similar initiatives in the devolved nations) and continued nurturance of relationships with industry. The UK may end up as a "rule-taker" most of the time. However, the UK is capable of excellence in several elements of paediatric clinical development, including PPIE, formulations, stratified medicine, and pharmacovigilance that is enhanced by population-based cohorts and understanding of genetic and mechanistic influences. Developing excellence will require continued, focused investment. The strong platforms for early-phase and late-phase studies need to be maintained. The UK's specific approach to reimbursing new medicines may not be compatible with contributing to a comprehensive pipeline of novel medicines for children. In any case, it is essential to develop the UK's reputation for efficient, effective, timely, and appropriate paediatric medicines development.

Table 1. Points to consider when evaluating the impact of Brexit on clinical development of medicines for children

Element of development	Goal	Current status with respect to goal[1]	Risks arising from Brexit	Aspirations / Opportunities for UK
Identification of therapeutic need	Match effective product to a profitable market that reflects a therapeutic need	Patchy: identification of therapeutic need has not been not a success of the current framework	UK needs are not considered in global decision-making	Therapeutic needs could be identified based on needs of people, and reimbursement issues, as well as current approaches
Plan drug development	Feasible plan that minimises risks and burdens arising from research, including avoiding studies that do not contribute useful information	Good, but some weaknesses	UK not sufficiently strong to influence design of programmes or studies	Promote provision of reliable information to support preparation and feasibility of programmes and studies, (including ethical, legal and social issues) based on infrastructure, record linkage, clinical expertise and input from children, young people and their families
Formulations	Appropriate for age and capability of the recipient of the medicine	Partial	Market size, import/export issues	Make the most of own licensing arrangements, e.g. Specials
Clinical trial approvals	Timely, proportionate review by people with relevant expertise	Patchy across Europe		Build on first-mover advantage for integrated approvals (need to consistently exceed European standards) Specific expertise, e.g. pooling neonatal ethics review and other specialist areas
Exploratory / Early phase trials	Informative, acceptable, well-conducted studies	Patchy	Business goes elsewhere	Build on infrastructure to ensure consistently efficient and high-quality delivery
Confirmatory / Late phase trials	Informative, acceptable, well-conducted studies	Patchy	Business goes elsewhere	Build on infrastructure to ensure consistently efficient and high-quality delivery
Marketing Authorisation	Timely, appropriate decisions	Standardised timelines	Increased overheads (time and direct costs) for Sponsors reduces choice and/or adds delays	Efficient decisions that promote UK public health
Available	Reasonable price	Patchy across Europe. UK has delays	Less leverage	Balance needs for access to costs of access to meet specific UK needs
Used effectively	Right drug, right person, right time	Poor across Europe; NICE guidelines have impact in the UK	Minimal: UK systems for quality health care stand alone	Maintain and develop high standards
Surveillance	Timely, well evidenced information about concerns	Generally good	Loss of some links with international comparators	Continued development of "enhanced" PV (records linkage; mechanisms; pharmacogenomics/ stratified medicines) that is informative to the rest of the world through compatibility with global reporting systems

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A PATIENT AND FAMILY PERSPECTIVE ON EARLY ACCESS TO MEDICINES

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There was a collective sigh of relief as the little baby girl was born. Her first gasp and cry already entwined with the unbounded hopes and dreams of her parents. A mere 14 days later, they would be inundated with medical terminology, explaining the life-limiting condition their little bundle of joy was suffering from. Terminology they would hear repeatedly and apprehensively – spinal muscular atrophy. This was their little girl, 46 chromosomes of perfection, and yet, the genes had played afoul. They were now left to try and right the wrong, making decisions to improve her quality of life, if at all.

The overhead theatre lights at the research centre shone bright, dispersing the helplessness they felt. As 'dad' held her hand, she received intrathecal injections of Nusinersen. This would be one of many monthly injections that he would hold her through. In late 2016, Nusinersen became the first of its kind to be approved to treat the spinal muscular atrophy. With preliminary clinical trial results showing remarkable outcomes, this medication is now accessible through the expanded access programme on the NHS. News that came as a blessing for this little girl and her parents. The lack of knowledge of long-term side effects did dim their happiness a little bit. But they would face that hurdle as it came, for now she would serve as a beacon for those to come.

It is a hope and not a cure, and this they are acutely aware of. They are determined to give her "any chance she can get", and the expanded access programme was exactly that. They recognise and are grateful for those parents and children through whom this hope exists.

As my time with them ends, she raises her arm towards me. It would be easy to take that for granted, if not for the ventilatory support machine that sits near her head. "She's developing quite a personality", dad states proudly a small smile playing at his lips. Her first birthday now only a couple of months away.

FIND OUT MORE...

The parents featured in this article would like to thank the Sick Children's Trust for organising accommodation, a home away from home, during these testing times. If you would like to contribute, towards the Sick Children's Trust, to help parents in a similar situation, please donate below: https://www.facebook.com/donate/2155809284746210/?fundraiser_source=external_url

THE NIHR CLINICAL RESEARCH NETWORK FOR CHILDREN: SUPPORTING THE BEST RESEARCH FOR CHILDREN AND YOUNG PEOPLE

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The National Institute of Health Research was established in 2006 to help research to reach its full potential in the NHS[1] following the publication of 'Best Research for Best Health: a new national health research strategy' setting out how the NHS in England was contribute to health research[2]. Prior to this, paediatric research was prioritised by the UK government for substantial investment as part of the strategy on Medicines for Children in 2004. A key component of this strategy was in 2005 to establish Medicines for Children Research Network (MCRN) (funded by the then Department of Health and subsequently adopted by the National Institute for Health Research [NIHR] as part of the Clinical Research Network [CRN]), which coincided with the introduction of the European Commission Regulation on Medicinal Products for Paediatric Use which came into force in 2007[3]. The development of these regulations was a landmark step for paediatric medicines development including requirements for all new licensing applications to include age-specific paediatric investigation plans (PIP), with information about safety and efficacy of medicines, and detailed information about age-appropriate formulations.

The scientific evidence generated from clinical trials, pharmacokinetic studies and studies of drug toxicity need to be applied in order to ensure that medicines are used rationally in children[4]. This includes the evaluation of drug efficacy, toxicity and metabolism. The MCRN provided an established network to support commercial and non-commercial studies supporting the development of age-appropriate medicines for children[3]. As part of the activity of the MCRN, 14 subspecialty groups were established called Clinical Studies Groups (CSGs) providing multidisciplinary clinical and academic expertise that included patients and family representatives and expertise in pharmacy. The CSGs support investigators and the pharmaceutical industry in the planning, development and delivery of new studies, identify areas of unmet need for drug development and provide advice about paediatric formulations and regulatory issues in relation to paediatric drug trials. In 2009 the MCRN was joined by the NIHR Comprehensive CRN Paediatric (non-medicines) Specialty Group (PSG) supporting a national portfolio of paediatric research studies that did not involve medicines. Subsequently the NIHR underwent significant reconfiguration in 2014 with the fundamental remit of improving access to research for clinicians, academics and patients across the country[5]. This reconfiguration brought together the MCRN and PSG to form the NIHR CRN Children's Specialty. The new CRN structure incorporates 15 Local CRNs (LCRNs) across England along with a single national co-ordinating centre. Thirty specialties are supported by each of the LCRNs, aiming to ensure the delivery of high quality research, equitable patient access and to ensure that studies are completed within well-defined timeframes.

NIHR supporting development and evaluation of paediatric medicines

NIHR CRN Children was established to support the evaluation of paediatric medicines in collaboration with industry. From the early days of the MCRN, NIHR CRN Children maintains a close working relationship with industry and other bodies governing paediatric medicines research supporting early and late phase clinical trials, pharmacokinetic, pharmacodynamic, pharmacovigilance and other high-quality studies with a recent focus on stratified medicine and technology for child health.

The CSGs linked to NIHR CRN Children play an important role in the development of paediatric pharmaceutical studies, by providing advice about research protocols to industry relating to the delivery of each study in the UK, the accessible patient population and the barriers to delivery. This includes issues such as drug delivery, the limitation of blood sampling in smaller patients to avoid complications and frequency of visits[6]. To facilitate implementation of paediatric clinical studies on the NIHR portfolio, each LCRN has a Children's Specialty Lead (supported by the National Children's Specialty Lead) who works with a regional research team to ensure the effective delivery of research studies within the NHS. Fundamental to the delivery of paediatric clinical studies are the established UK-wide Clinical Research Facilities (CRFs). In the last 5 years there has been an increase in the number of paediatric CRFs, and paediatric beds within CRFs demonstrating the increasing awareness of having appropriate space to deliver paediatric early and late phase trials. The NIHR CRN also provides infrastructure support for centres that may play a role in the development of medicines and diagnostics, including the Biomedical Research Centres (BRCs), Translational Research Collaborations (TRCs) and MedTech & In-vitro diagnostic Cooperatives (MICs), thus spanning the pathway of invention, evaluation and adoption.

NIHR CRN Children and regulation

The significant extent of off-label and unlicensed drug use in the paediatric population has led to legislative changes in the USA and Europe to govern the study of paediatric medicines[7]. Prior to the introduction of European legislation in 2007, an estimated 50% of medicines used in children had never undergone a clinical trial in a paediatric population raising concerns about toxicity and side-effects[8]. The EU Directive (2001/20/EC) on Good Clinical Practice for Clinical Trials was adopted in April 2001, and came fully into force in May 2004. This Directive takes into account some specific concerns and provides criteria about performing clinical trials in children. On 29 September 2004, the European Commission released the first proposal for a Regulation on medicinal products for paediatric use. On 27 December 2006 the Regulation was published in the Official Journal of the European Union and entered into force on 26 January 2007[9]. The objective of the Paediatric Regulation is to improve the development of high quality and ethically researched medicines for children up to 17 years, to facilitate the availability of information on the use of medicines for children, without subjecting children to unnecessary trials, or delaying the authorisation of medicines for use in adults. The NIHR CRN Children has played an important role in supporting the development and implementation of these regulations across Europe as a member of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). The pharmaceutical industry has also been incentivised with a 6-month patent extension to medicines (extension of the duration of its Supplementary Protection Certificate) on the grounds that trials involving children carry a paediatric investigation plan (PIP). For medicines that are no longer patent protected, a period of market exclusivity (a Paediatric Use Marketing Authorisation—PUMA) can be provided. Pharmaceutical companies are asked to prepare and submit a PIP at the end of phase I or II pharmacological studies. Every PIP presented by industry must be submitted to the Paediatric Committee (PDCO) of the European Medicines Agency (EMA)

The NIHR Children's Portfolio

NIHR CRN Children oversees and supports a significant number of studies. In 2017/18, 44,414 participants (figure 1) were recruited to studies where the managing specialty was Children, with a further 81,780 participants recruited to studies for which the Children's Specialty provided support. Due to the complexity of commercial studies and due to the fact that many deal with rare diseases in children, 1050 patients in 137 studies were recruited to the commercial studies during the same reporting period. Figure 2 demonstrates the continuing growth in the number of commercial studies in the life sciences sector recruiting children.

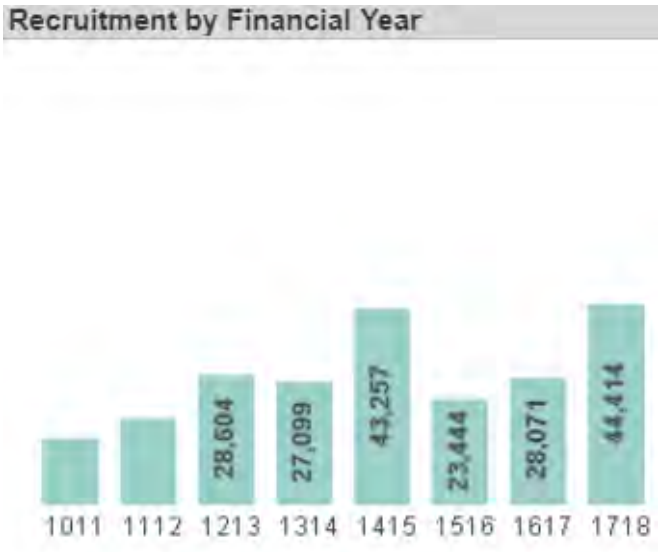

Figure 1: Number of patients recruited to NIHR Children's portfolio studies in each financial year from 2010/11

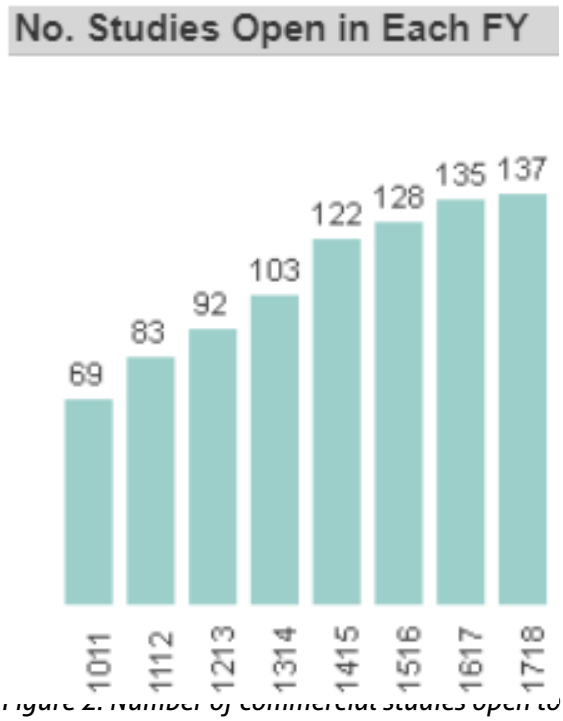

Figure 2: Number of commercial studies open to recruitment in each financial year from 2010/11

Future developments in NIHR CRN Children

As we move into a new era of stratified medicine otherwise known as personalised or precision medicine, NIHR CRN Children alongside other specialties has focussed on the key elements required to carry out world-leading stratified medicine research, including comprehensive and linked genotypic and phenotypic patient data, expertise in the discovery, development and validation of biomarkers and diagnostics, access to well characterised cohorts of patients, and the ability to design and deliver stratified approaches in both early and later phase clinical trials. Implicit in this process is the collaboration between the NIHR CRN, BRCs, MICs, Translational Research Collaborations, UK Biobanks, Experimental Cancer Medicine Centres and Industry. Thus, the stratified medicine agenda will drive novel clinical drug trials to enable the identification and development of treatments that are effective for particular groups of patients, and direct the appropriate timing of therapy.

In January 2018 the NIHR Children & Young People MedTech Cooperative was launched to support the development and evaluation of technology for child health. Whilst not directly related to drug development, advances are being made in drug delivery devices to provide a more effective way of delivering medication and monitoring compliance (e.g. smart inhalers).

Finally, following six-year project funding by the European Innovative Medicines Initiative 2, conect4children (collaborative network for European clinical trials for children, c4c) is a large collaborative paediatric network that has been established that will facilitate the development of new drugs and other therapies for the entire paediatric population in Europe. The c4c consortium aims to enhance the competitiveness of Europe as a critical region for developing medicines for children by using existing expertise, patient access and developing common processes to be applied to disease natural history studies, registries, studies of new therapies and comparisons of existing therapies[10].

Overall, despite the currently challenging political environment of Brexit, a promising future lies ahead for the development and regulation of paediatric medicines, particularly with the joined-up approach across Europe to support paediatric clinical drug trials, and the infrastructure support to advance paediatric drug delivery. Moving forward we must continue to ensure that children remain safe and are treated appropriately during clinical drug trials, that their voice is heard and that we continue to foster a coordinated approach to overcome challenges and get the best and most advanced treatments for children. After all, our future depends on them.

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FPM NEWS

AN INTERVIEW WITH INCOMING PRESIDENT OF THE FPM PROFESSOR TIM HIGENBOTTAM

CONSULTATION ROUND-UP

We have been busy with a number of consultations recently, mainly around the theme of Brexit.

On the 15th Oct we submitted a response via the Academy of Medical Royal Colleges to the House of Commons Health and Social Care Committee inquiry into the Impact of a No-Deal Brexit on Health and Social Care.

We are currently also in the process of responding to the MHRA inquiry on EU Exit no-deal contingency legislation for the regulation of medicines and medical devices.

DR DAVID BLOWERS
10 APRIL 1948 - 11 OCTOBER 2018

It is with great sadness that we report the passing away of Dr David Blowers. David was a practical and well-grounded pharmaceutical physician. His career started with a 10 yr stretch in big pharma, rapidly being promoted to VP International Medical Affairs at SmithKline Beecham, followed by more than 20 yr consulting career that spearheaded pharmaceutical physician support to the burgeoning number of biotechs. He had an exceptional work ethic and an innate sense of the standards he expected of himself and of others.

This translated into a deep and long-standing commitment to training and career development through the professional bodies in his field, and particularly to the Faculty, of which he was one of the original Fellows, and the new specialty of pharmaceutical medicine, with its specialist certification training. Moreover, these personal attributes and clear-sighted vision enabled him to influence greatly in its formative years the development and recognition of this medical specialty. He not only supported the Faculty itself but raised the profile of pharmaceutical medicine through University of Surrey training courses.

His work as a specialty adviser and Director of CPD brought him into regular contact with all the stakeholders in the specialty training programme. There are many pharmaceutical physicians who have David to thank for his encouragement as well as critical and professional advice, moderated with entertaining good humour, helping them towards their own career goals.

David was an irrepressible character, passionate and professional, who until very recently worked tirelessly for the Faculty and for BrAPP, and his sad loss is felt deeply amongst his many friends and colleagues.

by Dr Flic Gabbay and Professor Peter Stonier

PMST CURRICULUM 2020

KONRAD OBIORA
SPECIALTY TRAINING MANAGER

The FPM launched its PMST Curriculum 2020 Project at a meeting of the Curriculum and Assessment Working Group (CAWG) on 13 September 2018. The purpose of the project is to write a new curriculum for the Pharmaceutical Medicine Specialty Training (PMST) programme, which must be approved by the GMC in 2019 and implemented in 2020. We are delighted that 53 FPM members volunteered to help complete this project.

The project follows an independent review called the Shape of Training Review that was led by Professor David Greenaway. Professor Greenaway's report – *Securing the future of excellent patient care* - made several recommendations to change postgraduate medical education and training in the UK to make training programmes more flexible for doctors in training and to ensure that doctors have the required skills and capabilities to meet patient and health service needs.

All the UK royal colleges and faculties are in the process of writing new curricula. The new curricula must include specialty-specific capabilities and incorporate the GMC's Generic Professional Capabilities (GPC).

The FPM will consult key PMST groups on the proposed specialty-specific capabilities in practice (CiPs) and GPCs for pharmaceutical medicine in Spring 2019.

EDUCATION DAY REPORTS

APPLYING ETHICAL VALUES AND GOOD PRACTICE IN PHARMACEUTICAL MEDICINE

12th JUNE 2018

DR CLAIRE BARTON FFPM
SPECIALTY ADVISER

I jumped at the chance to attend the FPM Education Day on 'Applying ethical values and good practice in pharmaceutical medicine', thinking that the topics would be fascinating and eager to hear of others' experiences. The event lived up to my expectations, with introductory sessions by Professor Alan Cribb and Philippa Foster Back CBE that were informative and thought-provoking, but also highly entertaining. The workshops I attended ('Integrity and safety in drug development' and 'Standing your ground on professional values') were lively and interactive, and it was particularly interesting to work on real dilemmas that the facilitators had faced in the past. So, after our groups had thrashed out our views and proposals, we were then able to hear what happened and the final outcomes. We also learned a useful framework for identifying conflicting values, and techniques to use to stand our ground, and we practiced these using role play and scenarios. These techniques will undoubtedly prove useful in the future for dealing with difficult interpersonal interactions, regardless of whether an ethical issue is at stake. As in previous FPM Education Days, the number of delegates was just right for meeting the speakers and facilitators, making new contacts and catching up with old friends and colleagues.

Voxpops from FPM Education Da

DR TEMITOPE ADELOYE
PMST TRAINEE

The day kicked off with a breakfast briefing led by two P
of working as pharmaceutical physicians and provided
preparation for the Diploma in Pharmaceutical Medicin
other trainees: it helps you avoid common pitfalls and
will help me as I progress through my own training. The r
sessions and workshops broken up by a tea/coffee bre
discussion with other delegates and session leaders
pharmaceutical medicine' and 'Integrity and safety in dru
we were given real-life cases of potential safety signals
of questions to explore how we would investigate tho
experience in the collection of adverse events during
including design of safety studies in the post-marketin

ay 2018

JOHN POSNER FFPM
BOARD MEMBER
DIRECTOR, HUMAN PHARMACOLOGY PROGRAMMES

The event was a sell-out with over 90 members attending; I had the feeling that the subject matter was of real interest to all of us present. I shall limit my comments to the one part of the day's programme that made the most impact on me. It was the morning workshop entitled 'Integrity and Safety in Drug Development' introduced by Drs Josh Brostoff and Alastair Benbow. We were told about a drug in early clinical development for HIV in which adverse events suggestive of a hypersensitivity reaction had been noted in a small percentage of patients receiving the drug. At the time, it was suggested that the reaction might be associated with particular genomics. The question that we were asked to address was whether to investigate the pharmacogenomics of patients participating in a clinical trial. To me the answer was obviously 'yes' so I was surprised to hear expressed a range of opinions in the room. One argument against further investigation was that it might compromise the integrity of the study but all agreed that the double-blind could easily be maintained by allowing only a Data Safety Committee access to the treatment code. More seriously, there were concerns about perhaps unnecessarily excluding patients shown to have certain genetics. Furthermore, such testing would only be of benefit to a small proportion of patients but might become a requirement before using the drug in routine practice making it too expensive for poorer countries where HIV is so prevalent. These issues had been raised at the time the drug was developed and it had taken perseverance of the physicians concerned to overcome opposition. The case demonstrated beautifully how necessary it is for pharmaceutical physicians to study ethical values.

PMST trainees. They shared some of their experiences
helpful tips on how best to approach ePortfolio and
e. It is always useful to learn from the experiences of
there were things I took away from that session that
est of the day was filled with a combination of didactic
eak and lunch, and there was ample opportunity for
s. I attended two workshops: 'Emerging issues in
ug development'. I found the latter particularly useful:
s and were asked, in groups, to work through a series
se signals. As a research physician I have hands-on
a trial, but this workshop covered a broader context,
g setting.

THE VACCINE RACE

A BOOK REVIEW BY ALICE KAY
POLICY AND COMMUNICATIONS GROUP

> "*Developing vaccines is probably one of the most productive things you can do, simply because if you succeed in getting one made, you watch a disease disappear.*"
> Alan Shaw, formerly of Merck.

This remarkable and gripping story of the development of the first safe, effective vaccines against rubella, polio, measles, and rabies, is an absolute must-read. Nowadays, it is easy to take for granted that we are protected against a myriad of infectious diseases that once killed people by the thousand. This book serves as a timely reminder of how remarkable vaccines have been in relegating those scourges to history.

Meredith Wadman takes a complex and competitive period in the history of medicine and distils it down into a thoroughly enjoyable, fast-paced march through a time of outstanding scientific discovery and genuine medical breakthroughs. She deftly combines detailed descriptions of ground-breaking experiments taking place in laboratories across the USA and the world with personal, and at times touching, anecdotes of the human scientists driving this revolution. Behind the scientists, the key protagonists of this book are a culture of human cells produced in the Wistar Institute in Philadelphia: WI-38. From their controversial origins in the lungs of a Swedish aborted foetus, to their acceptance as the best way to produce safe vaccines, to the bitter dispute over their ownership, the fortunes of these cells are traced over the decades as they — eventually — prove to be the 'holy grail' that pharmaceutical companies needed to produce safe and effective vaccines.

Wadman sets the scene at a time when numerous infectious diseases posed life-or-death threats to much of the population, but especially vulnerable babies and children. She reports how rubella (also known as German measles) led to thousands of women seeking often-illegal abortions after contracting infections during pregnancy. Thousands more had to face the tragedy of giving birth to children with severe congenital defects to their hearts, eyes, and ears, and too many children had to endure being unable to see, hear, or run around with their peers.

In addition to rubella, polio, measles, and rabies (which was rampant in many animal populations) all posed significant threats to people round the world, and many of the available vaccines of the time were crude and ineffective at best, and potentially harmful at worst. One of the most prevalent risks from vaccines came from the cells they were produced in, many of which were monkey kidney cells that harboured a plethora of harmful viruses that could infect vaccine recipients. Vaccine developers and regulators knew of many of these dangers (though in some cases they were reluctant to acknowledge the problem) but few safe alternatives were available.

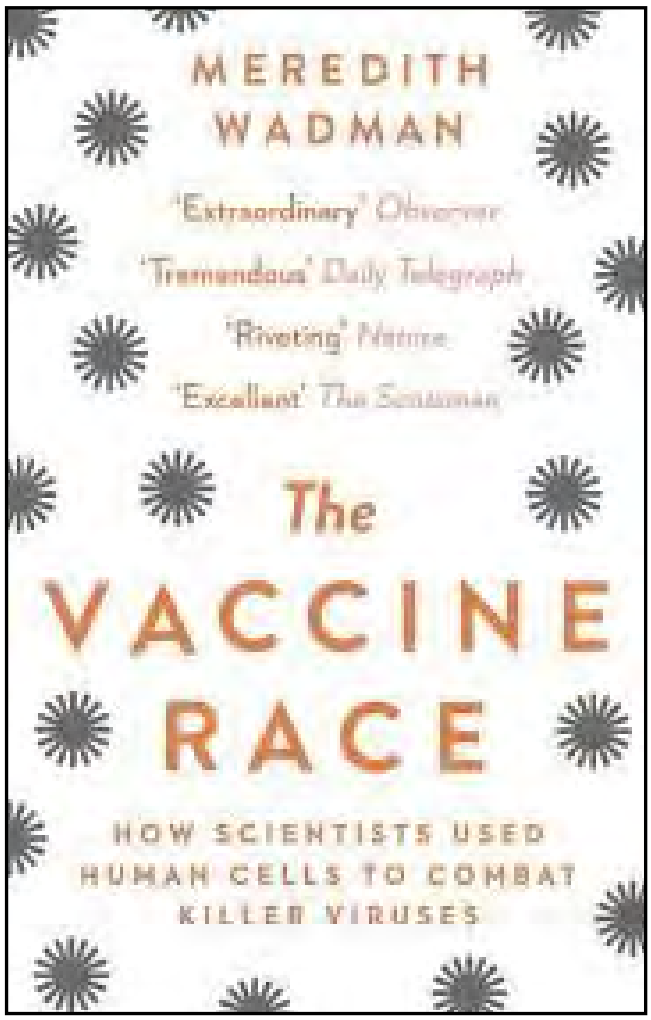
Against this backdrop, it would seem logical that research indicating that virus-free human cells could be safely grown in the lab and used to produce weakened viruses for vaccines would be greeted with great enthusiasm. Yet when Leonard Hayflick, the creator of WI-38 cells, demonstrated just that, the response from the community was lacklustre to say the least. Hayflick spent the next decade doggedly trying to convince the scientific community in the USA — and most critically of all, pharmaceutical companies and the vaccine regulator — that his WI-38 cells were far more suitable to developing vaccines than monkey kidney or duck embryo cells. WI-38 cells were used in European countries, but the US regulator adopted an ultraconservative stance and effectively blocked the use of WI-38 in vaccine development in America. For vaccine developers, who were in a desperate race to produce and licence effective measles, rubella, and rabies vaccines, there was no incentive to switch to these cells from established animal cell lines, no matter the risks. Indeed, there was sustained resistance to the safe and effective rubella vaccine developed by Hayflick's colleague Stanley Plotkin and produced in WI-38 cells. Wadman traces Plotkin's stubborn fight — as dogged as Hayflick's — to licence his vaccine despite competition from far more powerful rivals. The experiences of these two men and many other researchers demonstrated that power, personality, and politics were key influences in the vaccine race.

An intriguing aspect explored in the latter half of the book involves the relationship between science and profit, and whether discoveries should be patented and commercialised. Hayflick himself sparked controversy by charging institutes and companies for access to his WI-38 cells, and experienced a backlash from many colleagues who held the traditional view that science should purely be about knowledge and not money.

More shocking are the descriptions of experiments and trials testing new vaccines that would fall foul of all modern ethical committees. Premature babies were administered experimental polio vaccine, while an untried rubella vaccine was given to the residents of a home for young children with intellectual disabilities — neither group could provide informed consent. Such trials were a product of the time and undoubtedly sped along the development of such important vaccines, but they do cause one to stop and ponder the risks taken by participants (knowingly or unknowingly) for the benefit of the wider population.

One criticism that could be made is the somewhat selective focus on American science; it is clear that progress in the vaccine race was being made elsewhere in the world, but many developments are only briefly mentioned before Wadman returns to the scene in the States. Given the international nature of science and the collaborative efforts to develop vaccines, it's the shame the spotlight was not shone on the more international aspects of the story.

Although we know the happy outcome of the vaccine race, this book illustrates the challenges of scientific progress eloquently and engagingly. What truly resonates with the reader are the personal efforts and sacrifices of the researchers and clinicians who made these vaccines a reality and helped to protect billions of people worldwide from devastating diseases. A quote from Alan Schmaljohn from the University of Maryland sums it up best: "*Vaccinology, I would say that's not rocket science. It's a lot harder than rocket science.*"



PAEDIATRIC PREVENAR 13 STUDY IN THE UK

DR SUE TANSEY
VP AND GLOBAL HEAD OF THERAPEUTIC STRATEGY ARIDV AND WOMEN'S HEALTH
THERAPEUTIC STRATEGY & SCIENCE UNIT
IQVIA

From October 2006 to October 2008, when I was employed as a pharmaceutical physician at Wyeth Vaccines, I was the medical monitor for a randomized, double-blind, controlled UK study in infants that we conducted with our investigational 13-valent pneumococcal conjugate vaccine PCV13.[1] Prevenar 13 is the approved name for PCV13, which was developed by Wyeth to improve protection beyond that provided by the licensed 7-valent pneumococcal conjugate vaccine PCV, since pneumococcal infection including invasive disease such as septicaemia and meningitis has a high morbidity and mortality in young children and infants.

In the period 2000-2006 there were 54.2 cases of invasive pneumococcal disease (IPD) per 100,000 children in the UK.[2] There are over 90 strains or serotypes of the pneumococcus. Prior to introduction of PCV7 the only available vaccine against pneumococcal disease was a polysaccharide vaccine that was not recommended in infants since their immature immune systems tend not to respond to it. Conjugate vaccines such as PCV7 and PCV13 consist of polysaccharides conjugated to an immunogenic protein and are thus able to elicit an immune response in infants and young children including a memory response.

PCV 13 contained serotype 1, 3, 4, 5, 6A, 6B 7F, 9V, 14, 18C, 19A, 19F, and 23F polysaccharides individually conjugated to **CRM_{197}**. Wyeth wanted to evaluate PCV13 in accordance with the UK immunisation schedule in place at that time so we conducted a study in several UK sites comparing PCV13 with PCV7 in healthy infants in a 2-, 4-, and 12-month schedule.

This study took place across 9 UK sites, the majority of which were part of the **UK Paediatric Vaccines Group** (see details below). Potential participants were identified either via child health computer databases or directly by general practitioners. Healthy 6- to 14- week infants were enrolled.

Two hundred and eighty-six healthy infants were randomized to receive PCV13 or PCV7 at 2, 4, and 12 months of age, alongside a serogroup C meningococcal (MenC) vaccine (2 and 4 months of age), diphtheria, tetanus, acellular pertussis, polio and haemophilus influenza type b vaccine (DTaP-IPV-Hib 2, 3, and 4 months), and a Hib-MenC vaccine (12 months).

Following the clinical development of PCV7 the **WHO recommended an immunological correlate of protection for efficacy**[3] against pneumococcal invasive disease. This avoids the need for large efficacy studies in the development of subsequent pneumococcal conjugate vaccines, since due to practical and ethical considerations they could be impossible to conduct. Therefore, specific antibody responses were assessed by taking a blood sample from the infants at age 5, 12, and 13 months.

Concomitant vaccine immunogenicity was evaluated 1 month after the infant series at 5 months of age using standard enzyme linked immunosorbent assay (ELISA) techniques.

Local reactions and systemic events were collected by an e-diary completed by the parent/caregiver for 7 days after each vaccination. Other adverse events observed were collected in the case report form.

The pneumococcal immune response was shown to be comparable for the 7 serotypes shared between PCV 7 and PCV 13. For PCV 13 there were excellent responses against the additional 6 serotypes and these antibodies were shown to be functional by opsonophagocytic assays.

The percentages of infants that achieved pre-specified antibody concentrations thresholds for immune response against haemophilus influenzae type B, meningococcus C and pertussis antigens after the infant immunization were similar in both groups with over 96% participants in both groups achieving accepted prespecified thresholds for MenC and Hib.

Local and systemic events were similar in the two groups and there were no serious adverse events considered to be related to the vaccine or conduct of the study by the investigator.

In summary, the results of the study showed that a 2,4 and 12-month course of PCV 13 was immunogenic, well tolerated and did not interfere with the immunogenicity of the concomitantly administered routine immunizations.

This UK study was submitted to the EMA as part of the marketing authorisation submission for PCV 13. PCV13 was subsequently granted a marketing authorisation from the European Medicines Agency and introduced into the UK immunisation schedule in 2010 replacing PCV7 which had been added in 2006.

The data from this study was not only important for the UK but also relevant to other countries that have adopted a 2-dose priming and single dose booster schedule for pneumococcal vaccination and showed that a higher valency pneumococcal vaccine had potential to extend protection against pneumococcal disease to a wider range of serotypes. In addition to Prevenar 13, there is a licensed 10-valent pneumococcal conjugate vaccine available in the UK that is manufactured by GSK.

Public Health England (PHE) manages the largest national IPD dataset in the world, with around 5000 annual reports of IPD from England and Wales, of which more than 90 % are serotyped. Therefore, we have data to monitor the impact of pneumococcal vaccination on the number of cases of IPD and the serotypes causing them. Data published in 2015 4 showed that 4 years after introduction of PCV 13, overall IPD had been reduced by 56% compared with the pre-PCV7 baseline. However, the data showed that most IPD cases are now due to non-PCV13 serotypes emphasizing the need for higher valency or serotype-independent vaccines in the future. The pharmaceutical industry is already working to develop those next generation vaccines.

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CRM_{197} A non toxic mutant of diphtheria toxin used as a carrier protein/adjuvant

The UK Paediatric Vaccine Group (UKPVG) works as a clinical trials network and has been conducting both industry- and publicly-funded trials of vaccines in children and young adults for nearly 20 years. More recently the academic centres involved (Oxford Vaccine Group, Bristol Children's Vaccine Centre, Manchester Children's Hospital, University of Southampton and St. George's Medical School in London) have joined the newly constituted National Immunisation Schedule Evaluation Consortium (NISEC) which undertakes studies on behalf of the UK Department of Health and in response to policy questions raised by the Joint Committee for Vaccines and Immunisation (JCVI), the UK National Immunisation Technical Advisory Group.

WHO recommended correlate of protection: As recommended by the WHO, a pneumococcal serotype-specific serum IgG concentration of ≥0.35 µg/mL serves as a reference value or correlate of protection for efficacy against pneumococcal invasive disease.

PAEDIATRIC INVESTIGATION PLANS – ADDRESSING KEY CLINICAL ISSUES

DR PETER HESSION
INDEPENDENT PHARMACEUTICAL PHYSICIAN
MEDIPLEX LTD

Introduction

The paediatric investigation plan (PIP) was introduced into the regulation of medicines in the EU in 2007. Its aim is to ensure research is performed that leads to the authorisation of medicines for use in children. The background, legal basis, processes and outcomes of PIPs are described in detail on the website of the European Medicines Agency (EMA).[1]

A PIP, or a waiver from performing a PIP in all or some paediatric age groups, must be agreed with the EMA by the time of the marketing authorisation application for a new medicine (in adults and/or children), or by the time of an application to add a new indication, pharmaceutical form or route of administration for a patent-protected medicine already authorised in the EU. If one or more 'deferrals' have been agreed, it is not necessary to have completed all or some of the plan at this time, or perhaps to have even started it. A lack of agreement will result in the marketing application not being validated; this emphasises the importance of timely engagement in the PIP process, except for certain medicines that are outside its scope, such as generic products. The successes and challenges of the initiative have been reviewed recently. [2] A similar process is in place in the USA[3], but with significant differences, such as exclusion of products with an orphan designation, which are not excluded from the PIP process.

The focus of this article is on the key clinical issues that most benefit from the contribution of a pharmaceutical physician when the PIP application is being compiled. The EMA provides a useful template for writing the scientific parts of the application[4], which changes from time to time as the EMA's approach for presenting the arguments evolves. Of particular interest is Part B.1 ("Discussion on similarities and differences in the condition between populations, and pharmacological rationale"). Although this might seem to be merely a background section of the document, it merits close attention since it forms the basis for many later critical arguments.

The 'condition'

Part B.1 should define the 'condition' that will be the subject of the PIP application. This may be broader than the disease that is the subject of the planned indication in the marketing application, and this has important implications for the scope of the PIP and therefore the extent of any clinical trials that are included in it. How to define the 'condition' is discussed in detail in an EMA policy paper.[5] Briefly, if the medicine is expected (based on its mode of action) to have activity in any diseases outside of the planned indication and if there is unmet paediatric need in their treatment, the condition for the PIP should also encompass these diseases. However, to prevent the scope of the condition being too wide, any such diseases that are outside the High Level Term (HLT) in the Medical Dictionary for Regulatory Activities (MedDRA) that relates to the planned indication may be excluded from the condition. For example, if an adult indication is planned for essential hypertension but the medicine would be expected to be active in any type of systemic hypertension, the latter should be the condition, due to the unmet paediatric need in the treatment of secondary hypertension. However, even if the medicine might be effective in the treatment of pulmonary arterial hypertension, the condition would not have to cover this since it is not a type of systemic hypertension (which is represented by a HLT under which essential hypertension in classified in MedDRA).

Characterising the condition, its management, and the potential action of the medicine in it

Part B.1 of the application should also discuss any differences in the characteristics of the condition between children and adults, and between paediatric age groups (even though these are often poorly described), and how these differences might affect the mode of action of the medicine. This is often important in later establishing arguments for waivers in all or some paediatric age groups. One particularly important area of comparison is establishing whether the condition occurs in children; if it does not, this is one of the grounds for a waiver from a PIP in all children. Rarity of a disease in children (for example as found in a medicine with an orphan designation) is not an adequate basis for arguing that a condition does not occur in children; lack of occurrence must be supported by good evidence. Similarly, arguments for waivers from a PIP in certain paediatric age groups in which the condition does not occur must be well supported.

Part B.2 of the application concerns the current, accepted methods of treating (or preventing or diagnosing, if relevant) the condition in children in the EU, whether authorised or not. This leads onto a discussion in Part B.3 of the unmet therapeutic needs for the condition in the EU and the evidence available that the medicine might fulfil this need.

Proposing waivers and/or the paediatric investigation plan

The remainder of the application brings together the previous arguments in order to justify waivers from developing a PIP in all or some paediatric age groups (Part C) and, where necessary, proposes plans for a paediatric formulation (Part D.2), special non-clinical studies (typically on toxicity on juvenile animals) (Part D.3), clinical trials in children (Part D.4), and modelling/simulation or extrapolation studies to replace any of the latter (Part D.5). Arguments may be made to defer the start and/or completion of these measures in relation to the planned marketing application (Part E). The proposals in Part D should focus on the key elements that will become the binding elements in the PIP agreed with the EMA, and on justifying each of these elements.

Conclusion

The PIP application has become a central consideration, potentially on the critical path, in the development of many new medicines and major developments of authorised patent-protected medicines in the EU.

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GP TO RO: AN ECLECTIC JOURNEY

DR SUSAN BEWS
RESPONSIBLE OFFICER, FPM

Serendipity - *the occurrence and development of events by chance in a happy or beneficial way* – has certainly influenced my career. Where I am now was certainly never planned.

Like many, I joined pharma from general practice for the scientific challenge. It certainly provided that, but I had had little concept of the broad range of associated opportunities that would materialise and how fulfilling it would be. At that time Responsible Officers were not even a twinkle in anyone's eye; pharma promotion allowed teddy bears as promotional aids; the research centre of my French parent company (Sanofi) had carafes of cheap red wine on the canteen lunch tables - my French was always better in the afternoon. No personal computers or mobiles (bliss?) but the luxury of excellent secretaries.

Shortly after joining Sanofi UK I was very fortunate to have a relatively unusual opportunity for a Medical Director when we established the UK Clinical Research Centre in Wythenshawe on a green field site. Colleagues were much more helpful than during my GP training. Within a couple of years I had a large happy effective department with responsibility for Scandinavia and Australasia too. But then what was to become a familiar situation started, Sanofi acquired Sterling Winthrop and I took over their medical department in Guildford too and, now as Site Director, also the laboratories in Wythenshawe.

Then the bombshell came - I was instructed to close 'my' research centre as many of the functions were to be relocated to the US. Making redundant over one hundred and forty staff most of whom I had recruited (one only the day before I received the news) and then closing down a lovely purpose-built centre was tough but mitigated by the fact that so many staff successfully used the opportunity to further their careers. I had to relocate to the Guildford offices.

Serendipity from mergers and restructuring resulted in my joining Yamanouchi which became Astellas and then deciding, at yet another restructuring, that although I had loved my time in pharma throughout, it was time for something different.

Whilst in pharma I had been appointed to the Medicines Commission, the forerunner of the Commission on Human Medicines, and following that to its sister committee the Veterinary Products Committee, as a lay member, with a rapid induction to the hazards of sheep dips, the challenges of vaccinating fish, finding veterinary adverse reactions as fraught as for human medicines and site visits in wellies.

I realised that medical training and the extensive experience pharma provides form a sound background for broader lay roles and became a lay member with two professional regulators, the Bar Standards Board dealing with complaints against barristers and RICS in respect of surveyors. It was perhaps not surprising to realise the similarities in complaints and the issues underlying them between the various professions. Barristers, surveyors, doctors - there are many common threads in the professional and personal challenges we all face. Some cases necessitated inspections of barristers' chambers - experience of audits by the MHRA proved very beneficial!

In pharma I had always been interested in the regulatory side, enjoying the challenge of legally accommodating what was needed within a prescriptive landscape - perhaps I will be a lawyer in my next life. Serendipity had led to my first significant governance role which was on the board of a large housing association, a heavily regulated area, and shortly after to the board of the London School of Pharmacy. I additionally joined the board of two non-medical charities becoming more familiar with charity law too and was fortunate to be appointed to the board of the Solicitors Regulation Authority and chaired their Education and Training Committee.

In 2005, after leaving Astellas, I was elected as President of our Faculty which for me was a most privileged and fascinating time, during which I became treasurer of the Academy of Medical Royal Colleges (a role which continued after my presidency finished). When I became president, I had inherited an objective to undertake a full governance review – my other roles had given me a sound grounding for that review.

I had been involved with the Faculty since its inception having been on its inaugural board but had had to step away from a very active input for a period due to work pressures combined with roles at the ABPI/PMCPA including chairing the ABPI Medical Committee for ten years, a great forum to exchange ideas and learn. Throughout most of my pharma time I also served on what is now the Code of Practice Appeal Board. Early on, the documentation could be measured in feet and sometimes looked more like a new drug application in volume, but the PMCPA changed its procedures and documentation became more manageable. One other change that I really approved off was to ban smoking during the meetings. No longer did I have to arrive early enough to ensure that I found a seat a long way from the pipe smoking lawyer!

All these varied roles have eventually led to my current role as Responsible Officer for the Faculty. My first talks with the GMC about revalidation go back to my time with the ABPI Medical Committee. My diverse experiences have been instrumental throughout in discussions with the DH and GMC and then for shaping processes for ensuring that pharmaceutical physicians could revalidate alongside our clinical colleagues. Nearly twenty years and many iterations in gestation, revalidation is now established and a role that was not thought about when I took that first brave step to move into pharma is now a normal part of our vocabulary - although it is one I find quite difficult to explain to friends outside of medicine.

Do I have any advice? Yes! Take advantage of both the ups and downs that all careers bring. Realise that medicine is a superb training ground for activities beyond the traditional ones, look widely and have confidence to apply your knowledge and skills to contribute broadly and enjoy the resultant benefits. Also, if a job is not 'fun' (at least most of the time) then maybe it is time to change. You never know what is possible until you try, and serendipity plays a part in all our lives.

Do I have any regrets? Of course - that is only normal and my current one is one I cannot change: it is that due to the nature of our Designated Body I meet few of the six hundred doctors for whom I am RO and do not personally know many of our newer doctors. I do still however know a large proportion from my various previous roles and it is a pleasure to have been in contact with so many again, often after a very long time.

THE TYRANNY OF METRICS

A BOOK REVIEW BY DR FRED REID
POLICY AND COMMUNICATIONS GROUP

Given the title, one might be forgiven for suspecting the book was an extended rant of someone who was forced to submit to one metric too many. The book certainly has a polemic aspect. However, it is also much more than that. The author, Jerry Z. Muller, is a historian with an interest in social science, philosophy and capitalism. He explains that it was through chairing his academic department that he experienced the slow but relentless march and expansion of metrics within American universities. Whilst he does take time to dissect the true meaning of many metrics encountered in his own and other fields, usually finding them wanting, he is also interested in the underlying philosophy, in particular the ideas of transparency and accountability.

Muller sees much of the movement for metrics as descending from the industrial efficiency movement founded by the engineer Frederick Winslow Taylor who, in the early 20th century, analysed the factory production of pig iron. He advocated specialisation and standardisation of tasks, reporting of that activity and 'pecuniary carrots and sticks' and enforcing this system to improve production. The philosophy of measurement and reward spread to business schools, who produced general managers whose skills were not specific to particular industries, nor did they understand their nuances. 'If you can't measure it, you can't manage it'.

In the public sector this progressed further with metrics being made publicly available, so that organisations were transparent and that they could be held accountable by the general public (or their elected representatives). There then spawned the search for metrics that measured all that needed to be managed, as the limitations of these metrics became apparent, including how they were 'gamed', more and more sophisticated metrics were required. The collation of increasing amounts of data against more elaborate measures takes an ever-increasing amount of resource. Eventually culminating in 'obsessive measurement disorder'.

The author presents a variety of case studies of mis-measurement from academia and education, his 'home-turf', to healthcare, law enforcement, military counter-insurgency, finance and foreign aid. A recurring theme amongst his examples is the gap between what metrics purport, or are intended, to measure and what they actually measure. Increasing arrests and incarceration of drug dealers implies reducing supplies of illicit substances to the streets, but focusing away from 'kingpins' to the more numerous teenage dealers on the streets who are easily and quickly replaced may achieve no such reduction in supply.

Muller is also keen to emphasise the collateral effects of metrics and metrics-based rewards including, encouraging short-termism and deprioritisation of that which is not (perhaps cannot be) measured; and discouraging risk-taking (such as innovation) and cooperation. The final chapter is perhaps, to the readers of this review, the most important. The author provides a thoughtful checklist as to the proper use of metrics in management, a guide to aid avoiding the pitfalls he has explained.

Although the book is from one perspective an extended rant by a historian, it is also, from another perspective, very readable and contains thoughtful, even wise, advice.

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