Introduction to Tripartite Meeting Report (convenors: Dr Nigel Baber and Prof. Ros Smyth): Towards establishing optimal doses for drugs prescribed to children

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There is a widespread recognition among medical practitioners, politicians and society in general that children have been disadvantaged by being deprived of effective, safe and palatable medicines that have been investigated and regulated to the same standard as is the norm for adults. The reasons for this are complex and multifactorial. The overall burden of disease in children is much less than in adults and for many chronic diseases, diagnostic criteria are imprecise and outcomes difficult to measure. This means that it is more difficult to conduct high-quality studies in children following the same models used for adult studies. There is a perception that the market for most paediatric medicines is small and will not result in a return on investment, and that regulatory authorities are too demanding in their expectations of the quantity and quality of data in paediatric marketing authorization applications. Finally, there are concerns about the ethical difficulties associated with trials in children and associated procedures, such as blood sampling, for which consent from a third party (the parent), rather than the participant, is obtained.

It is also recognized that paediatricians and other healthcare professionals responsible for prescribing and administering medicines to children which have been based on less than ideal evidence of efficacy, safety and

quality, have done a remarkable job in relieving pain and suffering in their patients, without (though there are notable exceptions) major and catastrophic adverse events. However, this apparent safe use of medicines in children, especially in the long term, or when given repeatedly during periods of growth and organ development, may have occurred despite underdosing or overdosing, because adverse drug reactions may be subtle and difficult to detect, or because young children cannot report them.

Establishing the optimal dose or dose range for medicinal products is a fundamental principle of drug development and clinical practice. Achieving optimal dosing starts with exploratory studies and continues through pivotal clinical trials to the point of granting a marketing authorization. But the number of patients studied by then is, at best, several thousands and frequently far fewer. There are rarely safety data beyond a few weeks or months of exposure and even if the regulatory authorities grant a licence for a specific indication with the proviso of a post-approval commitment for post-marketing surveillance, there is a tension between the need to collect and analyse these long-term data, and the potential for over-zealous prescribing during this period.

Regulators, paediatricians, clinical pharmacologists, and pharmaceutical company technical staff with specific paediatrics drug development remit recognize the unsatisfactory situation and share a frustration in being unable to move forward in a co-ordinated way. As a contribution to the debate on dose optimization in children and to move towards some common understanding, the Medicines and Healthcare products Regulatory Agency (MHRA) initiated a 1-day tripartite meeting of invited experts from paediatrics, clinical pharmacology and clinical pharmacy, from the pharmaceutical industry and from the UK MHRA to address selected topics on dose selection for children. The specific aims the meeting was asked to address were:

- 1 To understand the current status of methodologies which may be used to estimate dose range in paediatric clinical trials.
- 2 To identify gaps in knowledge where further research is needed.
- 3 To consider strategies where safety issues related to under- or overdosing of medicines in children can be identified in post-marketing surveillance.

The meeting was hosted by the Association of British Pharmaceutical Industry (ABPI) and the complete set of presentations can be viewed via a hyperlink to the ABPI website. This supplement represents a summary of the presentations and some key aspects of the discussions which took place during the meeting.