GSK Public policy positions

Paediatric Medicines

The Issue

There is a recognised lack of medicines approved for children. This can result in one of two scenarios. Children are prescribed medicines approved only for adults according to a potentially inappropriate dose regimen or they simply do not get the medicines they need. Estimates for the US suggest that about two thirds of medicinal products that are prescribed for children have not been adequately studied and recommended for paediatric use.

There are long-established reasons for the lack of medicines with approved guidance on paediatric use. These include a number of ethical, practical, clinical and scientific challenges posed by conducting paediatric trials. However, in recent years there has been an increasing focus on addressing these challenges, highlighted in particular by the Millennium Development Goals which have called for a two thirds reduction in the number of deaths among under 5s between 1990 and 2015; the WHO's campaign "*make medicines child size*"; and legislative changes in the EU, mirroring an established incentives framework in the US.

This paper sets out GSK's longstanding commitment to developing paediatric medicines, including vaccines; details some of the complexities involved in their development; assesses legislative and other developments which have sought to address the hurdles; and sets out GSK's view on the challenges that still exist.

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GSK's Position

Our commitment

– GSK has an established commitment to researching and developing medicines, including vaccines, for children. Many of our medicines are recommended for paediatric use, including treatments for infectious diseases, asthma, cancer, epilepsy and eczema.

– GSK currently markets over 48 vaccines, 36 of which protect infants and children against illnesses such as chicken pox, diphtheria, tetanus, whooping cough, measles, meningitis, mumps, polio, hepatitis, rotavirus, gastroenteritis and rubella.

– GSK welcomed the WHO's "*make medicines child size*" campaign and Essential Medicines List for children launched in December 2007. It clearly identified the many challenges associated with the development and provision of paediatric medicines and the need for a partnership approach in response.

– In 2013 GSK formed an ambitious global partnership with Save the Children, with the aim of saving one million lives in five years using expertise, resources and fund-raising initiatives. Key features of the partnership include:

  – reformulation of the antiseptic chlorhexidine for cleansing the umbilical cord stump to prevent serious infection
  – developing and enabling access to affordable medicines to reduce mortality and newborn deaths
  – widening vaccination coverage to reduce the number of child deaths in the hardest to reach communities
  – evaluating new affordable nutritional products to help alleviate malnutrition in children
  – increasing investment in the training, reach and scope of health workers in the poorest communities to help reduce child mortality

– As part of our commitment to the Save Initiative GSK has formed a Maternal and Neonatal Health Unit. Its work includes the chlorhexidine reformulation and the development of novel treatment options for preterm labour.

– GSK has a proven record of providing medicines for diseases of the developing world, including paediatric indications. This work will often involve Public Private Partnerships (PPPs) which enable knowledge transfer and ensure our efforts have a tangible impact on addressing unmet medical need.

– GSK-sponsored paediatric clinical trials meet international and national regulatory and legislative requirements and follow the principles outlined in the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines.

– GSK makes the results of all clinical trials of our marketed products, including paediatric trials, available to healthcare practitioners and others who use or evaluate the use of our medicines via the GSK Clinical Study Register [http://www.gsk-clinicalstudyregister.com]. We also publicly disclose information on ongoing trials sponsored by GSK on www.clinicaltrials.gov.

The Role of Others

– GSK recognises the need for more paediatric research. We therefore welcome US and European incentive schemes that are intended to encourage more research into paediatric medicines. Incentives such as patent term extensions and extended marketing exclusivity help mitigate some of the complexities and additional costs associated with paediatric research.

– Initial industry experience of the relatively new (2007) European legislation, suggests that a review of some aspects of the scheme, including incentives, would be beneficial, to ensure that potential, largely bureaucratic, shortcomings are addressed. Nevertheless, GSK is confident that taken together, the EU and US legislation should help to ensure more paediatric research is undertaken into innovative treatments. We would urge other governments to follow the US and EU lead and introduce similar incentives.

– A number of affordable, effective, and well tolerated child-specific medicines already exist; however, they are not necessarily reaching the children who need them most. While the R&D industry has a key role in developing new medicines, other stakeholders must play their part in tackling the regulatory review, distribution and medical governance challenges associated with ensuring access to existing, not just future, paediatric therapies [1].

– Building on the scientific consensus agreed by the ICH in its Guidance on *Clinical Investigation of Medicinal Products in the Paediatric Population,* greater harmonisation of regulatory support for the development of paediatric medicines is required. Removing the need to address individual national/regional requirements would not only speed up paediatric research but, more importantly, it should help to ensure that unnecessary studies are not conducted. The "Paediatric Cluster" formed by the regulatory agencies of the EU, US, Japan and Canada could serve to help advance this goal. GSK also supports the greater alignment of the EU and US regulatory paediatric requirements that have been proposed as one of the areas to be considered in negotiations initiated in 2013 around a Transatlantic Trade and Investment Partnership.

– GSK is committed to conducting paediatric trials to high ethical standards and in a child-friendly fashion. We would however welcome more dialogue with regulatory agencies and ethics committees around the particular difficulties associated with conducting paediatric studies and how these are most appropriately reflected in the clinical trial design. Areas for discussion include the number of trial subjects in a particular age group (particularly for development work into rare diseases) and best practices related to blood sampling in paediatric populations.

– GSK recognises that an evidence-based approach may be unsuitable for the evaluation of pharmacokinetics, pharmacodynamics, safety and efficacy in some paediatric age groups and especially for rare diseases. We are therefore committed to using novel methodologies for evidence synthesis via modelling and simulation to support the development and approval of new medicines.

– A lack of regulatory capacity, particularly in many developing countries, is recognised as a challenge for ensuring the availability of paediatric medicines and child-friendly formulations. GSK works closely with other pharmaceutical companies to help build the necessary regulatory capacity across the developing world; however, more widespread mutual recognition of EMA and US approvals by developing country agencies would help to expedite access to new paediatric medicines.

[1] For instance, diarrhoea, which can easily be treated with oral rehydration salts plus zinc, still kills 1.9 million under-fives every year. Oral rehydration salts are easy to use, easy to manufacture and relatively inexpensive. They are also widely available in developing countries. Zinc, on the other hand, is not easily found in areas with a high incidence of diarrhoeal disease. Oral rehydration solution with zinc is more effective than without it.

– GSK is committed to continuously evaluating the benefit/risk profile of our medicines. We have policies and a global governance framework in place to help us detect and act on unexpected side effects that may be associated with the use of our medicines, including those used by children. However, GSK alone cannot address the pharmacovigilance challenges associated, in particular, with the treatment of children in the developing world. Improved collaboration between government, regulatory authorities, research institutions and the pharmaceutical industry is required to ensure that adequate safety monitoring and reporting systems are in place.

Background

The Challenges Associated with Paediatric Research and Development

The differences between children and adults in relation to medicines are well documented. Children differ in the way they ingest, absorb, metabolize and excrete drugs, and behavioural and developmental issues complicate their treatment. These factors are not constant but vary as the child grows and are reflected by the fact that "the paediatric population" comprises a number of broadly defined subsets, including preterm infants, newborn infants (0-27 days) infants & toddlers (28 days to 23 months), children (2-11 years) and adolescents (12 to 16-18 years, defined differently in different regions). Age-related differences mean that many medications have different therapeutic effects and adverse reactions in children compared with those in adults.

Doses for adults tend to be fairly uniform (mg) or normalised for differences in body weight, (mg/kg) without large differences between individuals. This implies that a limited number of tablet or capsule formulations and strengths of a medicine is sufficient to provide the appropriate adult dose. Children, however, have different physiology and may vary greatly in the way they respond to treatment. The need to generate and integrate evidence about the pharmacokinetics, efficacy and safety of novel medicines, including validation of age-appropriate and developmental outcome measures to reflect these differences, adds complexity and creates practical issues specific to paediatric research.

The lack of long term studies on the safety of drugs used in children can also present challenges for paediatric R&D. A September 2007 WHO Report, "*Promoting Safety of Medicines for Children*", estimated that less than 10% of all serious adverse reactions to medicines in children are reported globally. The fact that children are often less articulate in describing symptoms and that their non-verbal communication is often misunderstood or ignored, is one reason why adverse reactions will often go unreported to health practitioners or authorities. Furthermore, in a resource-limited setting, the lack of basic healthcare infrastructure and adequate pharmacovigilance training for healthcare professionals can undermine effective reporting.

Taken together, these practical, clinical and scientific issues can make evidence generation in paediatric research particularly challenging for both researchers and the regulators charged with reviewing and approving paediatric indications. Additionally, they are compounded by numerous ethical issues associated with the recruitment of children into clinical trials, including considerations associated with the assent and consent processes. Parents and carers can be reticent to expose their children to some of the perceived risks and inconveniences associated with full-scale clinical trials.

International Standards for Paediatric Research

ICH[2] Topic E 11 on *Clinical Investigation of Medicinal Products in the Paediatric Population* provides guidance on appropriate approaches to paediatric research. For example, when a product is to be used in children for the same indication(s) as those studied and approved in adults, the Guidance accepts that extrapolation from adult efficacy

[2] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990. It brings together the regulatory authorities of Europe, Japan and the United States, and experts from the pharmaceutical industry via the three regions' trade associations, plus key observers (including the WHO). The ICH's main purpose is to recommend ways of achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. Over 45 guidelines on a range of activities have been adopted since the ICH's creation.

data may be appropriate, making it unnecessary to conduct lengthy efficacy trials in children. In such cases, pharmacokinetic studies including the relevant paediatric population(s) likely to receive the product, together with safety studies, may provide adequate information needed by regulators to review and approve paediatric indications.

Similarly, when a medicinal product is to be used in younger children for the same indication(s) as those studied in older children, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger children, combined with pharmacokinetic study results, may be possible.

However, an approach based on pharmacokinetics alone is likely to be insufficient for products where blood levels are not well correlated with efficacy in adults or when differences exist in the pathophysiology of the disease in adults and children. In such cases, efficacy trials in children may be required. Efficacy studies are also expected when novel indications are considered for an existing product for which there is no evidence of safety and efficacy in children.

Efficacy Studies

The principles in study design, statistical considerations and choice of control groups that apply to adult studies generally also apply to paediatric efficacy studies. There are, however, certain features unique to paediatric studies which can introduce added complexity to the research process. For example, where efficacy studies are needed it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups.

Many regulators and Institutional Review Boards / Ethics Committees across the world reflect ICH Topic E 11 in their own approach to paediatric studies. This is increasingly helping to remove the need often to address individual national requirements which can not only speed up paediatric research but, more importantly, helps to ensure that unnecessary studies are not conducted. This scientific consensus is welcome and should be expanded wherever possible.

Paediatric Incentives

Notwithstanding the flexibilities reflected in the ICH Guidelines that have evolved to accommodate some of the challenges of paediatric research, the many scientific, ethical and practical complexities involved have traditionally made paediatric studies more costly and time-intensive than those conducted in adults. The market for paediatric medicines is inevitably also more limited than the adult market. As a result, there are far fewer paediatric indications than adult indications for medicines. GSK therefore welcomes the US and European incentive schemes that are intended to support more paediatric research and to protect the paediatric market.

US Legislation

In 1997, the US Congress enacted the Food and Drug Administration Modernization Act which included a provision, commonly referred to as the *Paediatric Exclusivity Provision* (PEP). Under this provision, the testing of medicines in children, if formally requested by the FDA via a Written Request, is rewarded by 6 additional month compound-specific market exclusivity on all approved indications. The additional period of exclusivity applies to all periods of patent-based or statutory (data exclusivity) protection.

In recognition of the PEP's success in generating a three-fold increase in the number of clinical trials planned, conducted or completed, the Best Pharmaceuticals for Children Act (BPCA), which effectively reauthorized PEP, was signed by President Bush in January 2002.

In addition to the BPCA, the FDA introduced the Paediatric Research Equity Act (PREA). Under the Act, sponsors submitting a new drug application ("NDA"), biological license application ("BLA"), or supplemental applications, must include "assessments" of safety and efficacy for all relevant paediatric populations for "claimed" indications. PREA allows FDA to require paediatric assessments for already marketed drugs in certain circumstances. PREA will only apply if the sponsor has refused to comply with a Written Request for paediatric studies under BPCA, and if the FDA certifies no funds are available for another entity to conduct the studies. Drugs and biological products that lack paediatric assessments within the time frames outlined in the Act may be considered misbranded. However, no criminal penalties apply.

Together, BPCA and PREA are generating a wealth of paediatric drug and research information for physicians, patients and parents. In July 2012 President Obama signed the Food and Drug Administration Safety and Innovation Act (FDASIA) into law, which permanently reauthorises BPCA and PREA. GSK supported their reauthorization. In addition, FDASIA also requires companies to submit a Paediatric Study Plan (PSP) within 60 days after an end-of-Phase II meeting or at such time as FDA agrees to, for a new active ingredient, new indication, new dosage form, new dosage regimen or new route of administration, which triggers PREA.

EU Legislation

The EU *Regulation on Medicinal Products for Paediatric Use* was incorporated into EU law in January 2007. It introduced the following key obligations, incentives and support:

– A new obligation on companies applying for marketing authorisation for new products, new formulations or new indications for patented products to conduct studies in children under the age of 18, in accordance with a Paediatric Investigation Plan (PIP). Alternatively, companies can apply for a "waiver" from this requirement for medicines unlikely to benefit children (eg. Alzheimer disease or breast cancer therapies)
– A provision for "deferrals" to ensure that medicines are tested in children only when it is safe to do so, but that in the meantime does not delay the authorisation of medicines for adults.
– A 6-month extension to the supplementary protection certificate (SPC) for non-orphan products in return for conducting studies in children in accordance with a PIP. For orphan products, extension of market exclusivity from 10 years to 12 years.
– An EU inventory of the therapeutic needs of children along with an EMA-based network of investigators and trial centres to conduct R&D into the development of medicines for children. The EU's Framework Programme offers funding for research into off-patent medicines.
– An expert Paediatric Committee within the European Medicines Agency (EMA) to assess and agree to companies' clinical research plans.

Initial experience with the European paediatric legislation has highlighted some – mostly practical and bureaucratic – areas that should, be reviewed and revised. For example, the content and expected early timing of submission of the initial PIP should be reconsidered, to allow the applicant to better define the details of the relevant paediatric programme at an appropriate time during development, and to better align with the equivalent submission in the US. The incentives should also be reviewed, to ensure that they meet the goal of encouraging paediatric research and development. For example, completed PIPs may not always lead to rewards, as the deadline for applying for a Supplementary Protection Certificate extension may not be achievable due to the length of certain paediatric development measures.

Off-Patent Paediatric Research

Both the US and EU paediatric legislation include provisions aimed at encouraging paediatric research on off-patent medicines.

– In the US, BPCA requires that the NIH - in consultation with FDA and experts in paediatric research - publishes an annual list of needs in paediatric therapeutics. The FDA can then issue a Written Request for paediatric studies of the off-patent drugs on the list. If the Written Request is declined by the application holder, NIH can fund the studies. If the additional work is accepted and undertaken by the application holder, on an off-patent drug, then financial compensation (rather than additional exclusivity) would be provided.
– In the EU, under a Paediatric Use Marketing Authorisation (PUMA) ten years data protection is theoretically available for off-patent products where a PIP is submitted, paediatric studies are conducted and an MA is granted. Unlike with applications for new products or revised applications for patented products for which PIPs are compulsory, companies may voluntarily decide to apply for a PUMA.

Paediatric Over-the-Counter (OTC) Medicines

It is generally recognised that the treatment of most childhood illnesses should be supervised by healthcare professionals in a clinical setting. Historically, this has meant that there has been limited demand for the development of paediatric OTC medicines from regulators or society. Relative to the number of clinical trials in adults, few clinical trials are, or have been, conducted for OTC products in children.

However, parents and caregivers understandably want to have some options available to treat the symptoms of minor illnesses in children (for example short term pain relief and fever control). GSK's Consumer Healthcare division offers a range of OTC products, some of which have a paediatric indication, for example Panadol and Zovirax Cold Sore Cream. Typically the regulatory approval of such OTC products for use in children is based on an ingredient's long history and usage in a wide population, including experience of its use in children in a prescription-only setting.

GSK does not routinely conduct paediatric studies as part of any OTC product development programme. If, however, there were a recognised need for a paediatric indication, it would be considered. In this respect, GSK welcomes the fact that the US legislation (BPCA) applies to any molecule that is the subject of one or more applications under Section 505. This includes OTC presentations approved under New Drug Applications, e.g., OTC switches. Under these circumstances, if GSK were to undertake paediatric studies on an OTC medicine then financial compensation (rather than additional exclusivity) would be provided by the NIH.

THE DEVELOPING WORLD CHALLENGE

The developing world presents its own set of problems associated with paediatric care, ranging from a lack of knowledge of what products have been developed; which are most appropriate for a developing world setting; the high costs associated with some paediatric formulations; the need to develop regulatory capacity in order to approve them; and how they should be prescribed and dispensed.

Essential Medicines List for Children

The WHO Essential Medicines List (EML) was first launched in 1977; however, while it included some dosage information for children, it was predominantly designed for adults. Recognizing this lack of child-specific medicines, the WHO published its first EML for Children in 2007. It has been updated several times since, most recently in 2013. It comprises over 270 medicines, including anti-AIDS treatments, vaccines, anaesthetics, hormones, vitamins and minerals; identifies further areas for review; and highlights existing gaps in paediatric medicines for a developing world setting. In 2013, 7.1% chlorhexidine digluconate for umbilical cord care was added to the EML. GSK's project to develop 7.1% chlorhexidine digluconate gel will facilitate access to this intervention in many countries in the developing world.

The EML for Children was the first step in a substantial WHO programme of work, under the global campaign – "*make medicines child size*". Also launched in 2007, the campaign is aimed at raising awareness and accelerating action to address three challenges associated with paediatric medicines, namely availability, accessibility and affordability.

The initial therapeutic focus of WHO's work is HIV/AIDS, malaria, tuberculosis, pneumonia and diarrhoeal diseases, which account for over 50% of under-five mortality. GSK (and our HIV collaboration with Pfizer, *ViiV Healthcare*) offers paediatric treatment or prevention options, or we are active in R&D, in all five therapy areas. In this way, GSK is committed to being an effective partner to WHO and other nongovernmental agencies that are involved in this paediatric initiative.

In 2010, the WHO published a Model Formulary for Children built on the EML that provides prescribing guidance on use of the essential medicines. As a result, for the first time medical practitioners worldwide have access to standardized information on the recommended use, dosage, adverse effects, and contraindications of these medicines for use in children.

Local Treatment Guidelines

Once appropriate and effective paediatric medicines are identified and research into the "gaps" is underway, the capacity to use them correctly needs to be assured. This involves ensuring that health workers know the appropriate ways to store, prescribe, dispense and administer medicines for children. Providing evidence-based prescribing information and guidelines at the point of care is an essential part of this strategy. The WHO has identified a lack of local guidelines as a major barrier to better paediatric healthcare. Developing countries are encouraged to develop local guidelines, using the WHO's treatment guidelines and 2010 Model Formulary as the basis for this approach.

Building Regulatory Capacity

The EML represents a valuable contribution to the promise of improved healthcare for children across the developing world. However, in helping governments to identify gaps in product registration, it also highlights the lack of regulatory capacity in a number of developing countries and how this can act as a barrier to access to paediatric therapies. As a global pharmaceutical company, GSK works closely with other companies to help build capacity in the regulatory area across the developing world. Examples include:

– Regional Regulatory Conferences: In collaboration with other members of EFPIA (the European Trade Association) and PhRMA (the Pharmaceutical Research and Manufacturers of America) GSK supports a series of annual regulatory conferences. The series began in 1996 with the Middle East Regulatory Conference and has been mirrored since in Asia and Latina (in collaboration with the International Trade Association, IFPMA). Representatives from the local and regional regulatory bodies are invited to hear regulators from ICH countries, as well as the R&D-based industry and the WHO, discuss best practice.
– Workshops: The Regional Conferences are supplemented by one-off workshops for Regulators on specific issues such as GMP and support for global clinical development. Again, representatives from ICH Regulatory Authorities, such as the FDA or EMA, are invited by industry to speak/train their counterparts in developing countries and thereby facilitate know-how transfer. Such workshops generally supported by industry, include organisation and some degree of funding.

GSK and Paediatric R&D into Diseases of the Developing World

GSK has an established track record of developing medicines for diseases for developing countries. Our R&D portfolio includes projects for a number of diseases of particular relevance to developing countries including: bacterial meningitis, Chagas disease, chlamydia, dengue fever, human African trypanosomiasis, leishmaniasis, malaria, pandemic flu, pneumococcal disease and TB.

GSK and PPPs

Many diseases, such as HIV/AIDS, affect both developed and developing world populations. Under these circumstances, the EU and US legislation should serve as a spur for more paediatric research of benefit to children in the developing world. However, many diseases only impact upon developing world communities who are least able to pay for desperately needed vaccines and medicines. Here, the market incentive to conduct paediatric research will not exist. Partnership, in the form of public-private partnerships (PPPs), is helping to address this challenge.

Ongoing GSK collaborations which involve – or will involve – the development of a paediatric indication include those with the Medicines for Malaria Venture (MMV), the Malaria Vaccine Initiative (MVI), the Global Alliance for TB Drug Development (TB Alliance), the Aeras Global TB Vaccine Foundation (Aeras) and the International AIDS Vaccine Initiative (IAVI).

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