LEADING ARTICLE

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Ethical, Regulatory and Scientific Challenges in Paediatric Drug Development

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Abstract

Drug development is a complex process that calls for the balancing of the requirements of a number of interests, including those of the pharmaceutical industry, regulatory authorities, science, ethics, politics and, not least, the patient. Originally the domain of academia, drug development is now performed by the pharmaceutical industry and controlled by regulatory authorities. It has created its own global frameworks, culminating in the International Conference on Harmonisation (ICH) regulations; for example, on good clinical practice (GCP) standards.

Over the last few decades, the demand for a stronger focus on drug treatment in children has developed from the voices of just a few paediatricians into action by governments and regulatory authorities.

The pendulum of scientific and ethical consensus has swung away from emphasizing the need to protect children against research. Children will always need protection in research; however, research to improve child health is now perceived as an ethical obligation and delays in passing benefits from pharmaceutical progress as unethical. The ethics of using child research to guide risk assessment in balance with the potential benefit to the single child, and children in general, is constantly evolving.

In 1997, the first successful paediatric legislation was introduced in the US and reduced the paediatric off-label use of medications primarily developed for adults. As part of the US Food and Drug Administration (FDA) Modernization Act (FDAMA) it offered an added period of patent protection to reward paediatric research. It was further complemented in 2003 by the Pediatric Research Equity Act (PREA) that made it a mandatory requirement for pharmaceutical companies to take children into consideration during the drug development process. FDAMA was re-authorized in 2002 as the Best Pharmaceuticals For Children Act (BPCA), and both acts, mandatory PREA and voluntary BPCA, were re-authorized in 2007 under the FDA Amendments Act (FDAAA) that also enacted new paediatric medical device provisions.

After many years of deliberation, an EU paediatric regulation came into force in 2007 that combines voluntary and mandatory aspects. Even more so than the US laws, this legislation emphasizes the need for the inclusion of children at an early stage of the drug development process. There is also increasing cooperation between the regulatory authorities in the US, EU and Japan with regard to the use of medicines in children.

Research into rare childhood diseases is facilitated by paediatric and orphan drug legislation. In addition, the health of children in the developing world is gaining higher visibility with the new World Health Organization campaign to "make medicines child size". Paediatric drug development is evolving as a complex process on the background of the globalization of trade, transport, travel, science, culture and politics. Continuing the dialogue between all partners in healthcare will be essential if an appropriate balance between risks, resources and benefits is to be reached.

Children in the developed world have never enjoyed better health and healthcare than they do today. Nevertheless, it is the scientific consensus that more needs to be done. In 1962, the US Kefauver-Harris amendments to the 1938 Food and Drug Cosmetic Act (FDCA) obliged manufacturers to prove the safety and efficacy of their medicines.[1] This led to the introduction of clinical testing in the modern sense, accompanied by the recall of thousands of prescription drugs from the US market.[2,3] It also

resulted in the introduction of disclaimers that stated that the respective drug had not been tested in children. In his criticism of these disclaimers, the American paediatrician Harry Shirkey coined the expression "therapeutic orphans" to describe children as being excluded from pharmaceutical progress.[4,5]

The sad irony was that both the 1938 FDCA and 1962 amendments had been prompted by tragedies that afflicted children: in 1936 more than 100 people died, one-third of whom were children, after ingesting a new liquid formulation of sulfanilamide,[6] and the 1962 amendments were triggered by thousands of children born with malformed extremities after their mothers took thalidomide during pregnancy.[7] The laudable determination of the US Food and Drug Administration (FDA) medical officer Frances O. Kelsey prevented the registration of thalidomide,[8] but it is little known that thousands of thalidomide samples were distributed in 'clinical trials' by medical practitioners following the suggestion of sales representatives, resulting in at least 12 children being born in the US with thalidomide malformations.[3,7] Today's sophisticated trial methodology, which includes emergency plans for the recall of trial medication, did not exist and it took the next few decades to reach an international consensus on the rules and principles that should be put in place.[9-12]

Between 1963 and 1997 there was a lot of lobbying, predominantly by clinical pharmacologists and pharmacists, at the national and international level to improve paediatric drug research, but the paediatric off-label use of drugs prevailed and is well documented in many publications and reports.[13-21]

History of art reflects our changed perception of children when we look at pictures from past centuries where children were dressed like miniature adults.[22,23] Progress in child medicine has its underlying developmental roots in academic research and clinical pharmacology. Academic research in child physiology has produced an ever increasing body of knowledge about the characteristics of the child's body as opposed to adults, leading to the famous and often repeated mantra that children "are not small adults".

Traditional mechanical formulas, based on bodyweight or body surface area, are frequently used to estimate doses for children but can lead to an under- or over-dose of medication. Clinical pharmacology has resulted in an increased understanding of the differences between adults and children and between the different age groups of children with regard to the absorption, distribution, metabolism and excretion (ADME) of drugs. The different components of ADME do not necessarily mature in parallel, nor do the different liver enzymes involved in metabolism. Depending on the main metabolic pathway(s) of the medication, extrapolation of adult data to adolescents may be possible, and from adolescents to younger age groups. Modelling and simulation can be of help in predicting the required dose and reduce the number of required patients per age group.

The International Conference on Harmonisation (ICH) *Tripartite Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population* (ICH E11) gives general guidance as to when extrapolation from adult data is acceptable and when proper clinical efficacy testing is required in the various child age groups.[10] For each individual drug in development, a careful case-by-case discussion will have to be conducted between the developing company and the respective national regulatory authority on the pediatric plan (FDA) and the pediatric investigation plan (PIP, European Medicines Agency [EMEA]).

The progress of clinical paediatrics has led to an increasing number of paediatric sub-specialties; as an example, the content page of the January 2008 edition of the *Journal of Pediatrics and Adolescent Medicine*[24] lists under "Advances in General Pediatrics" 48 headings from asthma therapy to viral laryngotracheitis. For those specialty areas where comparable diseases exist in adults, drugs are used that have predominantly been tested in adults.

1. Evolution of an Ethical Framework in Paediatric Research

In the early to mid 19th century, child health was discussed within the framework of women and children; that is to say not their genuine rights, but of society's social responsibility to protect the weak and vulnerable.[25] In many countries, women were still a century away from the right to vote. Until the 1960s, human experimentation was done by individual investigators, usually within the framework of academic institutions. Research in children was often performed on the researchers' own children, servants, slaves or orphans.[26,27] With the exceptions of Prussia in 1900 and Germany in 1931,[28] the ethics of scientific research in children was not addressed by governments or academic societies before World War II.

During and after World War II, medical research expanded at an extraordinary rate. After 1945 the world was outraged by the atrocities conducted in humans in general and specifically in children by Nazi physicians such as Josef Mengele[28,29] and by Japanese physicians in occupied China.[28] Following a critical evaluation of the observed wrongdoings and atrocities performed by Nazi physicians in Nuremberg, Germany, the judges who presided over the trial published a list of principles in 1947 that became known as the *Nuremberg Code*.[30,31] For the first time, this code promulgated a list of key issues in human experimentation.[13]

In 1948, the World Medical Association (WMA) adopted an international *Medical Code of Ethics*[32] in Geneva that asked members of the medical profession to have the utmost respect for human life. In 1949, in London, the WMA expanded this code to include the duties of the physician in general, who should always be "dedicated to providing competent medical service in full technical and moral independence, with compassion and respect for human dignity".[33]

Also in 1948, the General Assembly of the United Nations adopted and proclaimed the *Universal Declaration of Human Rights*;[34] children were specifically mentioned in article 25 (2): "Motherhood and childhood are entitled to special care and assistance. All children, whether born in or out of wedlock, shall enjoy the same social protection". In 1959 the UN General Assembly proclaimed the *Declaration of the Rights of the Child*.[35]

In 1964, the *Declaration of Helsinki* was adopted by the WMA at a meeting in Finland, which set out ethical principles for the medical community regarding clinical research in humans.[13,36] The term 'clinical research' replaced the term 'human experimentation' that was used in the *Nuremberg Code*. The *Declaration of Helsinki* is widely regarded as the cornerstone document of human research ethics although, as with the *Nuremberg Code*, it is not a legally binding instrument in international law.

Since 1964, the *Declaration of Helsinki* has been revised several times, and has become much more lengthy in order to address increasingly complex issues, such as the need for review of all biomedical research projects by an institution's review board (US) or ethics committee (other countries), the use of placebo, and research in developing versus developed countries.[13] As of May 2008, five revisions (1964, 1975, 1983, 1989 and 1996) and two clarifications (2002 and 2004) have been published by the WMA;[37] these revisions express the growing maturity of biomedical research and its increasing complexity within the divergence of a multitude of different interests and situations in a world that has increasingly become global and interlinked.

The decision by pharmaceutical manufacturers in the 1960s to introduce paediatric disclaimers reflects the framework of research that prevailed at that time. The development of medicines was the responsibility of chemists. The production of medicines was chemical manufacturing in those days, and the number of medical doctors working in the chemical industry was substantially less than the number that is employed in the area today.[3]

Outrage in the US after World War II did not lead to the application of the newly pronounced *Nuremberg Code* to experimentation in humans in general, or specifically in children; this took at least another 20 years. In 1966, Harvard anaesthesiologist Henry K. Beecher published a landmark paper that criticized 22 selected academic research projects that had been published in academic research journals and that were unethical in the view of the author. One of the quoted examples was the infection of mentally retarded children with hepatitis.[38,39]

Clinical trials in post-World War II North America were often performed in young male adult prisoners, and included the testing of toothpaste, deodorants, shampoo, skin creams, detergents, liquid diets, eye drops, foot powders and hair dyes.[40] In 1972, the *Washington Star* broke the story that the US Public Health Service (PHS) had been conducting a 'study' by observing untreated syphilis in Black men in Alabama, in and around the county seat of Tuskegee. Peter Buxtun, a PHS employee who majored in political science, had heard about the study from a coworker and, after making further enquires in 1966, worked toward getting the study terminated. Only when his attempts were rebuked by PHS management did he approach the press, in 1972. The Tuskegee study was terminated shortly after the *Washington Star* article;[41] however, it took a further 25 years before the US government officially apologized.[42] By the mid-1970s, the vast majority of medical experiments on institutionalized populations had been stopped in the US,[40] and a complex framework for the protection of subjects in human research began to evolve.

In 1973, the US Department of Health, Education and Welfare (HEW), which later changed its name to the Department of Health and Human Services (first referred to as the HHS and later as the DHHS), released the first set of proposed regulations concerning the protection of human subjects in biomedical and behavioural research, which were then published in 1974 as specific legal guidelines for clinical investigators (45 CFR 46; CFR stands for Code of Federal Regulations).[43,44]

In 1974, the US Congress established a National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research,[45,46] which, in 1978, published the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.[47] The report identified three basic ethical principles of particular relevance to the ethics of research on human subjects; these were respect for persons, beneficence and distributive justice.

- Respect for persons: individuals should be treated as autonomous agents, and persons with diminished autonomy are entitled to protection.
- Beneficence: persons should be treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their wellbeing. Specifically, research involving children is mentioned under this principle: "A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible,

while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices."

- Justice: the benefits of research and its burdens should be addressed in a sense of "fairness in distribution" or "what is deserved". An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly.[47]

The three main principles of the Belmont Report have undergone a change of meaning over the 30 years following their publication. A generation ago 'beneficence' was still perceived as characterizing the physician's personal characteristics, while today it is more seen as the individual's right to have the best choice within a vast array of therapeutic options. The concept of respect for persons has also changed, now meaning the patient's right to be treated as an autonomous person, for example to have the right to hear the truth about their medical condition, something that was not necessarily expected a generation ago.[48]

In 1977 the American Academy of Pediatrics published its first set of professional guidelines on the ethics of drug research;[49] these guidelines were updated in 1995.[50] Of interest is also their statement before the Institute of Medicine Committee on Clinical Research involving Children; 9 July 2003.[51]

In 1983, 10 years after the first proposals were outlined by the DHHS and 6 years after the National Commission's report on children,[52] the DHHS issued subpart D (*Additional Protections for Children Involved as Subjects in Research*)[53] to 45 CFR 46, after it had supplemented subpart B (*Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research*)[54] in 1978 with subpart C (*Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects*).[55]

In 1989, the United Nations issued a *Convention on the Rights of the Child* as a set of international principles setting out the civil, political, economic, social and cultural rights of children.[56] A child's right to enjoyment of the highest attainable standard of health is emphasized. The specific principles are: quality of care, freedom of choice, consent and self-determination, confidentiality, access to information, admission to hospital, health education, the dignity of the patient, protection from child abuse and religious assistance (i.e. the right to choose and practice a religion of your choice).

In 1990, the ICH was established as a working platform between the regulatory authorities of the US, Europe and Japan (the FDA, EMEA and Ministry of Health, Labour and Welfare [MHLW], respectively) and by the organizations representing the pharmaceutical industry in these three regions (the Pharmaceutical Research and Manufacturers of America [PhRMA], European Federation of Pharmaceutical Industries and Associations [EFPIA] and Japan Pharmaceutical Manufacturers Association [JPMA], respectively; under the umbrella of the International Federation of Pharmaceutical Manufacturers and Associations [IFPMA]), with several more regions represented as observers.[9] Of special interest in the context of this review are ICH documents E6 on good clinical practice (GCP)[10] and E11 on drug development in children.[11]

In 1991, a final *Federal Policy for the Protection of Human Subjects* was promulgated as "Common Rule" to integrate and consolidate the existing non-HHS governmental regulations on human subjects, then was accepted by the US Office of Science and Technology Policy and adopted by the DHHS and 16 other US federal departments and agencies.[57]

In 1997, the EU convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, the *Convention on Human Rights and Biomedicine* was promulgated in Oviedo, Spain.[58]

In 1998, the WMA adopted the *World Medical Association Declaration of Ottawa on the Rights of the Child to Health Care*,[59] the declaration refers to Article 24 of the 1989 United Nations *Convention on the Rights of the Child*.[56]

In 2000, ICH E11[11] was released to address the basic principles of when and how to develop drugs for use in the paediatric population.

In 2002, the Council for International Organizations of Medical Sciences (CIOMS) published a list of 21 guidelines within the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, among which was Guideline 14 on *Research involving Children*.[60]

In 2006, the EU *Ethical Considerations for Clinical Trials Performed in Children* were published on the EMEA website[61] for consultation, and the final version was released in 2008.[62] It is intended to work within the framework of the EU clinical trials directive,[63] which aims to harmonize the practice of GCP within all EU countries. The document starts with general, undisputed statements such as that children are not small adults and that as a vulnerable population they need protection against the risks of research but that this should not stop them from benefitting from research. The remainder of the document provides a compilation of EU and international documents that regulate clinical research in general and specifically clinical research in children. Definitions of key institutions as well as definitions such as ethics committees, age groups, informed consent and assent are also provided.

2. Regulatory Framework to Facilitate Paediatric Drug Research

2.1 US Paediatric Legislation

The subchapter entitled *The Need for Ethic Guidelines* from the 1977 American Academy of Pediatrics *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*[49] begins with the statement that "[s]tandards for performance of clinical pharmacologic research in infants and children must be established with the same humane purpose and scientific objectives as standards for clinical practice. Ethical practice requires that treatment modalities available to others be made available to pediatric patients, and that, as for other subjects, appropriate protection be given to pediatric patients when they receive treatment." In 1979 the FDA introduced a paediatric subsection and in 1994 a paediatric labelling requirement.[15] Neither measure resulted in a major advance in paediatric drug research.

In 1997 the FDA Modernization Act (FDAMA) introduced a voluntary incentive for the pharmaceutical industry in the form of an added 6 months market exclusivity (called 'Pediatric Exclusivity') against generic competition (section 111 of the FDAMA).[64] Companies were granted Pediatric Exclusivity if they fulfilled the terms of the Written Request[1] issued by the FDA. The FDAMA was so successful that it was re-authorized in 2002 as the Best Pharmaceuticals for Children Act (BPCA) and extended until the end of September 2007.[65,66]

In 2003 the FDAMA was supplemented by the *Pediatric Research Equity Act* (PREA),[67] which gave the FDA authority to request the paediatric assessment of new drugs and to compel pharmaceutical companies to undertake paediatric development in the same indications as in adults. The PREA was ratified after the 1998 Pediatric Rule was struck down by a federal court after claims that the FDA had overstepped its authority.[68-70] As the PREA replaced the original Pediatric Rule, it was applied retrospectively to its original timeframe; that is, all submissions on or after 1 April 1999.[68,70] The PREA makes it mandatory for pharmaceutical companies to submit a paediatric assessment for each age group in the case of medicines filed for regulatory approval in the US (unless a deferral or waiver have been granted). A paediatric assessment contains the data from the paediatric studies for which the assessment is required. A paediatric plan, which is a statement of intent that outlines the paediatric studies the company plans to conduct, should be discussed with the FDA at pre-investigational new drug (pre-IND) and end-of-phase I meetings for products intended for the treatment of life-threatening or severely debilitating illnesses; for drugs intended for all other diseases, the paediatric plan should be submitted and discussed no later than the end-of-phase II meeting.

Both the PREA and BPCA legislation were re-authorized in 2007 as Titles IV and V of the FDA Amendments Act (FDAAA) with a few modifications.[70] The FDAMA and BPCA are regarded by the FDA as the one single measure that contributed to an exponential increase in paediatric pharmaceutical clinical research.

A list of all drugs for which a Written Request has been issued and those for which Pediatric Exclusivity has been granted is published on the FDA paediatric website;[71] this list contains a considerable proportion of all modern patent-protected medicines. The clinical investigations stimulated by FDAMA/BPCA were pharmacokinetic-pharmacodynamic studies, dose adjustments in younger age groups, safety and efficacy, new indications and contra-indications. The investigated indications range from the same indication as in adults, such as the investigation of antihypertensives in paediatric hypertension,[72] to rare diseases that affect mostly children, such as the investigation of alendronate in osteogenesis imperfecta,[73] tamoxifen in McCune-Albright syndrome[74,75] and sildenafil in neonatal pulmonary hypertension.[76] In the last few years, the FDA has increasingly asked for the development of paediatric formulations. Experience with the PREA is still limited, as it has only been in force for 5 years.

2.2 EU Paediatric Regulation

Drug treatment of children in Europe was comparable to the situation in the US before the introduction of the US paediatric legislation in 1997 and 1998[15,77] as documented in numerous publications.[16-21] Discussions on paediatric legislation began in Europe on an EU level in 1997 as a roundtable discussion within the facilities of the EMEA.[78] It took 10 years until it was finally published in December 2006 in the official EU journal as a 19-page document (in the English version), and came into force in January 2007.[79,80]

The EU Paediatric Regulation is a piece of legislation that combines both voluntary and mandatory aspects of paediatric drug development. As a reward for compliance, it offers 6 months of added market exclusivity in the form of a supplementary protection certificate (SPC). In EU countries, a SPC is a *sui generis*, patent-like, intellectual property right, available for drug, and plant, protection products, granted in compensation for the long development time required to bring new pharmacological agents

1 A 'Written Request' is a document in which the US FDA explains the research expected for a specific drug. Once the company has declared its agreement to the Written Request and submitted the generated data, it is entitled to 6 months of paediatric exclusivity.

to market.[81] See table I for the structure of the EU Paediatric Regulation.

The EMEA Paediatric Committee (officially abbreviated to PDCO) was constituted in July 2007 in order to oversee implementation of the EU Paediatric Regulation,[82] and subsequently took over the duties that had previously been entrusted to the EMEA/Committee for Medicinal Products for Human Use (CHMP) Paediatric Expert Group.[83] The PDCO now assesses all PIPs, waivers and deferrals.

The composition of the PDCO aims at representing scientific, regulatory and healthcare professional knowledge in all aspects of paediatric drug development. The Committee is composed of one representative for each EU Member State (there are currently 27 Member States) plus one alternate for each state representative. Furthermore, three representatives from healthcare professions and three representatives from patient advocacy groups will become PDCO members during 2008.[82,84] The pharmaceutical industry is not represented in the PDCO, but regular meetings are arranged with a group of industry regulatory affairs associates through the EU pharmaceutical industry's trade association, the EFPIA.[85]

Table I. EU Paediatric Regulation: structure/table of contents[81]

Section	Article number
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While the Paediatric Regulation officially came into force at the beginning of 2007, the introduction of the requirements have been staggered. From 26 July 2008, a condition of registering a new drug is the requirement for paediatric data based on an agreed PIP ("the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan"), or a PDCO-approved waiver or deferral. In other words, the EU regulation regards the availability of paediatric data reflecting an entire preclinical and clinical development as standard at submission, unless the EMEA has granted a waiver or deferral (article 7). The PIP has to be submitted no later than the end of pharmacokinetic studies. From 26 January 2009, this requirement also applies to the submission of new indications, new pharmaceutical formulations and/or new routes of administration for already registered drugs, if they are patent-protected or protected by an EU SPC (article 8).[77-88] Of course, for drugs that are already registered, the PIP submission will be long after the end of the pharmacokinetic studies. However, any company that plans to file for approval of a new indication is well advised to submit the PIP in due course in order not to put at risk the validation of the newly submitted indication.

As mentioned previously, compliance with the PIP will be rewarded by 6 months of additional market exclusivity in the form of a prolongation of the SPC.[89] To allow the generics industry to prepare for this SPC extension, data generated in compliance with the PIP must be submitted to the EMEA 2 years before the expiry of the SPC. However, as a transitional measure until 2012, the PIP data can be submitted 6 months before SPC expiry.

With the introduction of the EU paediatric regulation, the EMEA will give scientific advice for paediatric development questions free of charge.[89-91] Key elements of submitted PIPs, as well as the details and results of clinical trials performed in children, will be made public on the EMEA website after deletion of commercially confidential data. The Paediatric Regulation also enforces the existing pharmacovigilance activity of the EU and will require risk management plans where appropriate.[92]

For orphan drugs, the 10 years of marketing protection is extended to 12 years if paediatric development is performed (article 37), and for off-patent drugs a special paediatric-use

marketing authorization (PUMA) has been introduced.[93,94] Drugs with a specific paediatric authorization will be rewarded with 8 years of data protection and 10 years of marketing protection (article 38).[93,94]

Pre-existing paediatric clinical data on marketed drugs had to be submitted to the EU national competent authorities or the EMEA before 26 January 2008 (article 45).[94]

3. A First Appraisal of the EU Paediatric Regulation

While the US FDA view the US FDAMA/BPCA as a great success, drug development in children was not mandatory until 2003, so the Agency's experience in regulating research in children is still relatively limited. The first FDA review of PREA results took place in February 2008 and was presented to the Pediatric Advisory Committee; to date, 64 labels have been revised under the scheme.[95] Furthermore, discussion of a paediatric plan is strongly encouraged by the FDA, but the development company could, until recently, choose when to approach the FDA regarding paediatric issues. The EU regulation goes a step further in this regard.

For marketed drugs, a PIP must be completed with the submission of a new indication, route of administration or new formulation. For example, if a company wants to register a new formulation, it has to submit a PIP that covers all licensed indications. For each indication, the company has to explain age-group by age-group if the respective disease exists in children and to what degree a clinical investigation programme is feasible. If the drug is currently only in tablet form and the targeted disease also exists in children younger than 6 years old, the EMEA will request data on the development of a paediatric formulation as part of the PIP. As explained in the EU Commissions' PIP guideline,[96] the degree of accuracy expected in the PIP is rather high; the entire preclinical and clinical development programme should be outlined, unless the PDCO has granted a waiver or deferral. In the case of a deferral, studies and developments should be outlined in the PIP as far as it is possible to describe them at an early stage. Later, an amended PIP should be submitted with a more detailed outline.

For new drugs, companies are expected to submit a first PIP no later than the end of pharmacokinetic studies, as outlined in article 16 of the EU Paediatric Regulation (which refers to section 5.2.3 of Part I of Annex I to Directive 2001/83/EC).[97] In 2003, Directive 2001/83EC was amended by Directive 2003/63/EC[98] and this document contains section 5.2.3 of Part I of Annex I. At present, this is interpreted both by pharmaceutical companies and the regulators as corresponding roughly to the end of phase I. At the end of phase I, the available data in humans are those on first safety and pharmacokinetics. With the exception of oncology agents, no evidence of clinical efficacy will have been collected at this stage in the development process. At the end of phase I development, teams can do their paediatric homework, assess the frequency of the targeted disease in the different paediatric age groups and get an overview of existing alternative treatments.

Many development teams are currently in the process of preparing their first PIP for compounds that are now nearing the end of phase I studies. Over the next 18 months, we can expect there to be a steep learning curve for both the PDCO and the pharmaceutical companies, as they work towards balancing the early assessment of paediatric diseases and therapeutic alternatives, and the realistic planning of paediatric development. This balance should address all questions of preclinical testing, the need for juvenile animal testing, pharmacokinetics-pharmacodynamics, dose selection, paediatric clinical trials, paediatric pharmacovigilance and many other aspects.

Projects that have progressed beyond the end of phase I before June 2008 have some degree of freedom to decide when to submit a PIP to the EMEA. It is unlikely that the relevant planning and documentation will have been collated during the early development stage for these agents and will instead need to be added later in the drug development process, before a marketing application is filed.

In conclusion, the EU Paediatric Regulation will require the pharmaceutical industry to include children in their planning from an early stage of drug development. This is a huge challenge. Development teams need a basic understanding of the differences between adults and children, including disparities in:

- physiological factors
- organ maturation
- maturation of metabolic pathways
- maturation of excretion pathways
- psychological challenges towards parents, children and study personnel.

Every company is free to choose its approach to paediatric development. Some will build up a paediatric department, others will outsource as much as possible. But even if most work can be outsourced, key competence is required within the company to keep an overview and to supervise the outsourced work. Furthermore, each company needs internal policies, standard operating procedures (SOPs) and guidelines on how to deal with the requirements of paediatric drug development. As these are now legal requirements, no company has the choice of not complying.

It was paediatricians who first denounced the growing gap between the evolving development tools in the adult population and the makeshift approach that paediatricians had to maintain in the pharmaceutical treatment of children. Since 1997, when the

US FDAMA put paediatric drug development on the radar screen of top management within the pharmaceutical industry for the first time, and it became a mandatory requirement to include children in the drug development process in the US (PREA) as well as Europe, paediatricians and developmental clinical pharmacologists have been pushing for the inclusion of children in pharmaceutical research.

This is a new element in the drug development process as performed by the research-based pharmaceutical industry which is on one side heavily regulated and on the other follows the rules of the market. In contrast to FDAMA, where the potential return by extension of the patent life could easily be calculated, the reward for an inclusion of children in the early development process conferred by the EU Paediatric Regulations will be realized at the end of the patent life, i.e. 10–20 years after the end of phase I and only if the compound survives the attrition process.

It will take time to find a balance between the rights of children to benefit from pharmaceutical progress while not exposing them unnecessarily to compounds of which little is known. New development paradigms will also have to be tried and considered to address the question of the additional costs this will generate and how the additional testing should be financed.

4. Burden of Paediatric Legislation on Stakeholders

Without a doubt, paediatric legislation in both the US and Europe is increasing the workload of the regulatory authorities. The FDA has established its Office of Pediatric Therapeutics (OPT) and the EMEA has recruited extra staff to support the PDCO. The time invested by the members of the US Pediatric Advisory Committee (PAC) and the EU PDCO is considerable. The PDCO members' workload is emphasized frequently by individual members at national and international meetings.

The paediatric development plans first negotiated between the FDA and pharmaceutical companies following FDAMA in 1997 were short formless documents of a few pages in length. In contrast, the PIPs required by the EU regulation are complex and detailed documents. Their generation has caused a considerable increase in workload for drug company employees. There is general agreement between colleagues in pharmaceutical companies that the workload is immense. However, there are no statistics or estimates available to quantify this.

Beyond the burden caused by the generation of the paediatric plans (US) and PIPs (EU), there is also the impact of executing these plans to consider. While feedback on the first PIP submissions has been received from the PDCO and published on the EMEA website,[99] it is still too early to give even a tentative estimate on the extra work that will be generated by the preclinical, clinical, pharmacovigilance and other data described in the PIPs.

5. Scientific Challenges in Paediatric Drug Development

Neither the US paediatric legislation nor the EU Paediatric Regulation will fundamentally change the scope of drug development, which, over the last few decades, has become the domain of the pharmaceutical industry. Pharmaceutical companies develop drugs for unmet medical needs and require a return on their financial investment. A second source of innovation is inventions by academia or start-up companies that sell their new compounds for full clinical development, these compounds eventually entering into the global distribution and marketing process.

In the past, drugs developed primarily for the treatment of childhood diseases (e.g. lung surfactant for neonatal respiratory distress syndrome), have been tested in children; however, if the same disease existed in adults, the traditional approach was paediatric off-label use of drugs that had proven successful in adult treatment. While the off-label use of drugs in children will no doubt continue, the paediatric legislation has started to increase the quantity and quality of data available to the treating physician; a positive outcome that will only increase in the future.

It is also hoped that the new legislation, combined with modern drug development tools, will lead to an increased understanding of diseases that, although developing in childhood, are predominantly known in their mature adult chronic form. These include inflammatory and autoimmune diseases, such as asthma, rheumatoid arthritis and type 1 diabetes. In these diseases, the cascades that eventually lead to the mature form of the disease are increasingly well understood, but not yet well enough to prevent or cure the disease. It is hoped that science and drug development will eventually lead to the ability to interrupt this disease cascade and to prevent the development of the mature form of these diseases.

One area that holds great promise for paediatric drug development is gene technology, which allows the controlled production of human enzymes. Two examples of diseases that may benefit from gene technology are Gaucher disease (which often begins in childhood)[100] and Fabry disease;[101] both are conditions where the body is unable to produce a specific enzyme because of a genetic defect.[102] Another example is cystic fibrosis. Patients with this disease produce unusually thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections; it also obstructs the pancreas and prevents natural enzymes from breaking down and absorbing food.[103] In the 1950s, few children with cystic fibrosis reached elementary school. Today, many people with the disease live into their 30s, 40s and beyond.[103]

It is likely that neither the US nor EU paediatric legislation will lead to the development of new medications for diseases that occur exclusively in children. The US legislation has led to the investigation of adult medications in rare child diseases[104] and, hopefully, the EU regulation will have comparable outcomes in areas not covered by the US legislation, specifically biologics. Furthermore, in both the US and Europe, orphan disease legislation has successfully stimulated research into rare diseases.[105,106]

5.1 The Special Case of Paediatric Oncology

Paediatric oncology is a special case because it has the broadest gap between adult and child disease. Cancers in children are very different from that found in adults. While most adult solid cancers develop through decades of cell exposure to a noxious environment, paediatric solid cancers develop in young and very young cells.[107] The incidence of cancer in the paediatric population is also much lower than in the adult population.[108] In addition, although adult and childhood nonsolid cancers frequently have the same name, they are often biologically quite different. A third category are those cancer types that can develop between adolescence and early adulthood (e.g. Ewing sarcoma).

Paediatric cancer is not a uniform disease, but represents a multitude of different cancer types. As in adults, cancer treatment is based on a combination of chemotherapy, surgery and irradiation. The history of the treatment of childhood cancer is remarkable for the success of the last five decades through new regimens and combinations of drugs developed for adult cancer treatment, in combination with surgery and/or irradiation. Overall survival rates in child cancer have now reached ~75%.[109] This success has been achieved through paediatric oncology clinical research networks and often supported by medication from the pharmaceutical industry.

This therapeutic success is the best proof of the need for clinical trials in children,[110,111] as participating in a clinical trial has become the standard of care in paediatric oncology today.[112] Almost all drugs used in paediatric cancer treatment were approved for use in adults in the 1950s and 1960s.[108] FDAMA and BPCA have led to a multitude of paediatric investigations on substances developed for adult cancer. Usually, the FDA asked for early phase I and one phase II trial in paediatric cancer to grant paediatric exclusivity.[111]

Targeted medicines represent the next generation of therapy in adult anticancer treatments. As solid cancer types in children are very different from those for which targeted therapeutics were originally developed in adults, the place of these targeted medicines in paediatric cancer remains unclear.[113] The objective of future cancer drug research in children is to reduce the toxicity and morbidity surrounding the current medications, while maintaining the high survival rates seen in adults with the current treatment regimens.

The EMEA has published an addendum on paediatric oncology[114] to their *Note for Guidance on Evaluation of Anticancer Medicinal Products in Man*.[115] In Europe, the Innovative Therapies for Children with Cancer (ITCC)[116] and International Society of Paediatric Oncology (SIOP) Europe,[117] and in the US the National Cancer Institute[118,119] and the Children's Oncology Group (COG),[120] are the main groups that push for continuous improvements in paediatric cancer therapy, including preclinical testing and the continuous inclusion of newly developed medicines into paediatric cancer therapy.

Due to the low case numbers, divergence between adult and child cancer and differences in tumour biology, paediatric oncology probably represents the greatest scientific and regulatory challenge.

6. New Paths in Proof of Efficacy

The more we differentiate individual rare diseases or subdiseases into distinct types using modern diagnostic measures, the smaller the respective case numbers become. This poses increasing challenges as to the type of statistical evidence required by the regulatory authorities and used by pharmaceutical companies to prove the efficacy of new treatments. It is not possible to undertake double-blind, placebo-controlled studies involving several hundred patients per treatment arm in rare and very rare conditions. The EMEA guideline on clinical trials in small populations[121,122] represents a first step towards addressing this issue that certainly will be followed up in the continuous dialogue between industry, academia and the regulatory authorities.

6.1 Reimbursement and Paediatric Health Care

At present, pharmacological treatment of children is economic in comparison to adult medicines. Paediatricians and general practitioners currently often prescribe generics. In the future, reimbursement discussions for new drugs will probably also consider additional investments that have been necessary for paediatric research.

A considerable improvement in the availability of better medicines for children will inevitably lead to higher development costs and the question of how to offset this additional expenditure. One solution that has been successful for drugs developed for the adult market has been prolonged market exclusivity. Other models that have been discussed include 'transferable exclusivity' (i.e. paediatric research in drug A and a patent/SPC extension for drug B) and

the offer of preferential fast-track reviews by the regulatory authorities.

6.2 Academic Research and Paediatric Drug Development

It is often difficult to find industry sponsors for further analysis of off-patent medicines. In the US, a system is now in place where the National Institute of Child Health and Human Development (NICHD) issues competitive requests for proposals (RFPs) to solicit offerors capable of conducting studies of off-patent drugs for paediatric use information;[123] similarly, the *Seventh Research Framework Programme* (FP7)[124] plans to support paediatric research in the EU.

6.3 Paediatric Research Networks

Over recent years, a number of paediatric research networks have evolved to meet the challenges of paediatric research. Examples of these networks are of both a national/regional- and an indication-based nature, and include:

- the Pediatric Pharmacology Research Unit in the US;
- Medicines for Children Research Network[125] in both the UK and the Netherlands;[126]
- PAED-Net in Germany;[127]
- Finnish Investigators Network for Pediatric Medicines – FINPEDMED;[128]
- RIPPS (le Reseau d'Investigations Pédiatriques des Produits de Santé; Investigation Network for Paediatric Health Products) in France.[129]

Examples of indication-specific networks include the previously cited ITCC[116] and SIOP[117] in Europe for paediatric cancer, the Pediatric Rheumatology International Trials Organisation (PRINTO) network for paediatric rheumatology[130] and Paediatric European Network for Treatment of AIDS (PENTA) for paediatric HIV.[131] In addition, the Sixth EU Framework Programme is supporting the Taskforce in Europe for Drug Development in the Young (TEDDY).[132] In the future, one of the remits of the EMEA will be the coordination of a network of paediatric research networks.[133] There is almost an astronomical number of further national, international and global paediatric research networks and paediatric organizations.

In December 2007, the World Health Organization launched a global campaign to "make medicines child size".[134]

6.4 Recruitment of Children to Clinical Trials

When, in the 1960s, paediatric oncologists started clinical trials in children with cancer (testing higher doses of chemotherapy, new combinations of different cytotoxic agents and chemotherapy in combination with irradiation and surgery), they were accused of abusing children by using them as guinea pigs. However, over the last few decades, research in paediatric oncology has resulted in an overall increased survival rate in children with cancer to around 75% and, thus, its value in terms of survival and quality of life is much less disputed. For children with cancer, participation in clinical trials is today regarded as standard of care.

As a general rule, parents will allow the participation of their child in a clinical trial, and the more severe the condition of their child, the more hope they put into a novel treatment.

Convincing parents to include their child in a clinical trial must always be based on voluntary participation. Under no circumstances may the inclusion of a child in a clinical trial be facilitated by expensive gifts to the child or payments to the parents. Any compensation for work loss or travel expenses must be approved by the responsible ethics committee/institutional review board.

In addition to informed consent, which for children has to be signed by the child's parents as the legal guardians, today the assent of the child is required as soon as they are old enough to understand the nature of a trial. Usually, the age limit for this understanding is around 7 years old. A child that absolutely refuses to participate must not be recruited into a clinical trial.[135]

7. Conclusions

In recent years we have seen the issuance of new paediatric legislation in both Europe and the US, with the aim of creating better medicines for children and advancing current knowledge on drugs that are already used in this patient population. Paediatric drug development is a complex issue that revolves around the gravitational centres of science, regulatory authorities, business, politics and public opinion, to name but a few factors. Looking to the future, there will be many challenges for all stakeholders in this exciting area of drug development, and much work and dialogue will be needed for the best results to be achieved.

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References

1. US Food and Drug Administration. Overview and history of FDA and the Center for Food Safety and Applied Nutrition [online]. Available from URL: http://www.cfsan.fda.gov/~lrd/fdahist.html [Accessed 2008 May 13]
2. The story of the laws behind the labels. Part III: 1962 – drug amendments [online]. Available from URL: http://www.cfsan.fda.gov/~lrd/histor1b.html [Accessed 2008 May 13]
3. Hilts PJ. Protecting America's health. New York: Alfred A. Knopf, 2003

4. Shirkey H. Therapeutic orphans. Pediatrics 1968; 72: 119-20
5. Wilson JT. An update on the therapeutic orphan. Pediatrics 1999 Sep; 104 (3 Suppl.): 585-90
6. Wax P. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. Ann Intern Med 1995; 122: 456-61
7. Taussig HB. A study of the German outbreak of phocomelia. JAMA 1962; 180: 1106-14
8. US Food and Drug Administration. The story of the laws behind the labels. Part II: 1938 – The Federal Food, Drug, and Cosmetic Act [online]. Available from URL: http://www.cfsan.fda.gov/~lrd/histor1a.html [Accessed 2008 May 13]
9. International Conference on Harmonisation. History and future of ICH [online]. Available from URL: http://www.ich.org/cache/compo/276-254-1.html [Accessed 2008 May 13]
10. International Conference on Harmonisation. ICH tripartite guideline: guideline for good clinical practice – ICH E6(R1) [online]. Available from URL: http://www.ich.org/LOB/media/MEDIA482.pdf [Accessed 2008 May 13]
11. International Conference on Harmonisation. ICH tripartite guideline: clinical investigation of medicinal products in the pediatric population – ICH E11 [online]. Available from URL: http://www.ich.org/LOB/media/MEDIA487.pdf [Accessed 2008 May 13]
12. US Food and Drug Administration. FDA/NICHD conference. Clinical pharmacology during pregnancy: addressing clinical needs through science [online]. Available from URL: http://www.fda.gov/oc/speeches/2000/nichdconference12-4.html [Accessed 2008 May 13]
13. Golombek SG, van den Anker J, Rose K. Clinical trials in children: ethical and practical issues. Int J Pharm Med 2007; 21 (2): 121-9
14. US Food and Drug Administration. The pediatric exclusivity provision: status report to congress; 2001 Jan [online]. Available from URL: http://www.fda.gov/cder/pediatric/reportcong01.pdf [Accessed 2008 May 13]
15. Stoetter H. Paediatric drug development: historical background of regulatory initiatives. In: Rose K, van den Anker JN, editors. Guide to paediatric clinical research. Basel: Karger, 2007: 25-32
16. McIntyre J, Conroy S, Avery A, et al. Unlicensed and off label prescribing of drugs in general practice. Arch Dis Child 2000; 83: 498-501
17. Turner S, Longworth A, Nunn AJ, et al. Unlicensed and off label drug use in paediatric wards: prospective study. BMJ 1998; 316: 343-5
18. Ekins-Daukes S, Helms PJ, Taylor MW, et al. Off-label prescribing to children: attitudes and experience of general practitioners. Br J Clin Pharmacol 2005; 60 (2): 145-9
19. Conroy S, Choonara I, Impicciatore P, et al. Survey of unlicensed and off-label drug use in paediatric wards in five European countries. BMJ 2000; 320: 79-82
20. 't Jong GW, Vulto AG, de Hoog M, et al. Survey of the use of off-label and unlicensed drugs in a Dutch children's hospital. Pediatrics 2001; 108 (5): 1089-93
21. 't Jong GW, Eland IA, Sturkenboom MC, et al. Unlicensed and off label prescription of drugs to children: population based cohort study. BMJ 2002; 324: 1313-4
22. Liebenson B. ART; dressing children in a century past. New York Times 2000 Jan 9 [online]. Available from URL: http://query.nytimes.com/gst/fullpage.html?res=9402EFD6173BF93AA35752C0A9669C8B63 [Accessed 2008 May 13]
23. Museum of Fine Arts, Boston. Dressing up: children's fashions 1720-1920 [online]. Available from URL: http://www.mfa.org/exhibitions/sub.asp?key=15&subkey=654 [Accessed 2008 May 13]
24. J Pediatr Adol Med 2008 Jan; 9395 (76): [online]. Available from URL: http://www.medical-library.org/j_ped.htm [Accessed 2008 May 13]
25. Children's health and welfare. In: Encyclopaedia Britannica. Chicago (IL): Encyclopaedia Britannica, 1962
26. Lederer SE, Grodin MA. Historical overview: pediatric experimentation. In: Grodin MA, Glanth LH, editors. Children as research subjects: science, ethics, and law. New York: Oxford University Press, 1994: 3-25
27. Ross LF. Children in medical research: access versus protection. New York: Oxford University Press, 2006
28. Weyers W. The abuse of man: an illustrated history of dubious medical experimentation. New York: Ardor Scribendi, 2003: 161, 235
29. Mozes-Kor E. The Mengele twins and human experimentation. In: Annas GJ, Grodin MA, editors. The Nazi doctors and the Nuremberg Code: human rights in human experimentation. New York: Oxford University Press, 1992
30. National Institutes of Health. Regulations and ethical guidelines: directives for human experimentation [online]. Available from URL: http://ohsr.od.nih.gov/guidelines/nuremberg.html [Accessed 2008 May 13]
31. Nuremberg code [online]. Available from URL: http://www.hhs.gov/ohrp/references/nurcode.htm [Accessed 2008 May 13]
32. Declaration of Geneva, 1948 – the medical code of ethics [online]. Available from URL: http://www.donoharm.org.uk/gendecl.htm [Accessed 2008 May 13]
33. International code of medical ethics of the World Medical Association – 1949 [online]. Available from URL: http://www.cirp.org/library/ethics/intlcode/ [Accessed 2008 May 13]
34. United Nations. Universal declaration of human rights [online]. Available from URL: http://www.un.org/Overview/rights.html [Accessed 2008 May 13]
35. United Nations. Declaration of the rights of the child (1959) [online]. Available from URL: http://www.cirp.org/library/ethics/UN-declaration/ [Accessed 2008 May 13]
36. Human experimentation: code of ethics of the World Medical Association [online]. Available from URL: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1816102&blobtype=pdf [Accessed 2008 May 13]
37. Wikipedia. Declaration of Helsinki [online]. Available from URL: http://en.wikipedia.org/wiki/Declaration_of_Helsinki [Accessed 2008 May 13]
38. Beecher HK. Ethics and clinical research. N Engl J Med 1966; 274 (24): 1354-60
39. Krugman S. The Willowbrook hepatitis studies revisited: ethical aspects. Rev Infect Dis 1986; 8: 157-62
40. Hornblum AM. Acres of skin: human experiments at Holmesburg Prison. New York: Routledge, 1998
41. Jones JH. Bad blood: the Tuskegee syphilis experiment. New York: The Free Press, 1981
42. PBS Online. An apology 65 years late [online]. Available from URL: http://www.pbs.org/newshour/bb/health/may97/tuskegee_5-16.html [Accessed 2008 May 13]
43. US Department of Health and Human Services. Part 46: protection of human subjects. Section 46.103: assuring compliance with this policy – research conducted or supported by any Federal Department or Agency [online]. Available from URL: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.103 [Accessed 2008 May 13]
44. US Department of Health and Human Services, Office for Human Research Protections (OHRP). OHRP 45 CFR part 46 frequently asked questions (FAQs) [online]. Available from URL: http://www.hhs.gov/ohrp/45CFRpt46faq.html [Accessed 2008 May 13]
45. President's Council on Bioethics. Former bioethics commissions [online]. Available from URL: http://www.bioethics.gov/reports/past_commissions/index.html [Accessed 2008 May 13]
46. Field MJ, Behrman RE, editors. Ethical conduct of clinical research involving children. Washington, DC: Institute of Medicine of the National Academies, The National Academies Press, 2004
47. Regulations and ethical guidelines. The Belmont report: ethical principles and guidelines for the protection of human subjects of research [online]. Available from URL: http://ohsr.od.nih.gov/guidelines/belmont.html [Accessed 2008 May 13]
48. Cassell EJ. The principles of the Belmont Report: how have respect for persons, beneficence, and justice been applied in clinical medicine? In: Childress JF, Meslin EM, Shapiro HT, editors. Belmont revisited: ethical principles for research with human subjects. Washington, DC: Georgetown University Press, 2005
49. American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics 1977; 60 (1): 91-101 [online]. Available from URL: http://pediatrics.aappublications.org/cgi/reprint/60/1/91.pdf [Accessed 2008 May 26]
50. American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Pediatrics 1995; 95 (2): 286-94 [online]. Available from URL: http://pediatrics.aappublications.org/cgi/reprint/95/2/286.pdf [Accessed 2008 May 26]
51. American Academy of Pediatric/Society for Pediatric Research. Statement before the Institute of Medicine Committee on Clinical Research involving Children: participation and protection of children in clinical research. Presented: 2003 Jul 9 [online]. Available from URL: http://aps-spr.org/public_policy/2003_Docs/IOM0709.htm [Accessed 2008 May 26]

52. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Report and recommendations: research involving children [online]. Available from URL: http://bioethics.gov/reports/past_commissions/Research_involving_children.pdf [Accessed 2008 Jul 14]
53. Department of Health and Human Services. Code of Federal Regulations 45 – public welfare, part 46: protection of human subjects. Subpart D: additional protections for children involved as subjects in research [online]. Available from URL: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd [Accessed 2008 May 26]
54. Department of Health and Human Services. Code of Federal Regulations 45 – public welfare, part 46: protection of human subjects. Subpart B: additional protections for pregnant women, human fetuses and neonates involved in research [online]. Available from URL: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartb [Accessed 2008 May 26]
55. Department of Health and Human Services. Code of Federal Regulations 45 – public welfare, part 46: protection of human subjects. Subpart C: additional protections pertaining to biomedical and behavioral research involving prisoners as subjects [online]. Available from URL: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc [Accessed 2008 May 26]
56. United Nations. Convention on the rights of the child. Document A/RES/44/25, 1989 Dec 12 [online]. Available from URL: http://www.cirp.org/library/ethics/UN-convention/ [Accessed 2008 May 26]
57. Office for Human Research Protections. Common rule [online]. Available from URL: http://www.hhs.gov/ohrp/policy/#common [Accessed 2008 May 26]
58. Council of Europe. Convention on human rights and biomedicine [online]. Available from URL: http://www.worldcarecouncil.org/pdf/CoE_HRBioMed.pdf [Accessed 2008 May 26]
59. World Medical Association. World Medical Association declaration of Ottawa on the rights of the child to health care [online]. Available from URL: http://www.wma.net/e/policy/c4.htm [Accessed 2008 May 26]
60. Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects [online]. Available from URL: http://www.cioms.ch/frame_guidelines_nov_2002.htm [Accessed 2008 May 26]
61. EMEA. Ethical considerations for clinical trials performed in children. Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/paeds_ethics_consultation20060929.pdf [Accessed 2008 May 26]
62. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population: recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. Final 2008 [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical_considerations.pdf [Accessed 2008 Jul 14]
63. EU clinical trials directive. Directive 2001/20/EC of the European Parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [online]. Available from URL: http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf [Accessed 2008 May 26]
64. Food And Drug Administration Moderization Act of 1997: Public Law 105-115 [online]. Available from URL: http://www.fda.gov/cder/guidance/105-115.htm#SEC.%20111 [Accessed 2008 May 26]
65. US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry qualifying for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act [online]. Available from URL: http://www.fda.gov/cder/guidance/2891fnl.htm [Accessed 2008 May 26]
66. US Food and Drug Administration. Best pharmaceuticals for children act [online]. Available from URL: http://www.fda.gov/cder/pediatric/PL107-109.pdf [Accessed 2008 May 26]
67. US Food and Drug Administration. Pediatric research equity act of 2003 [online]. Available from URL: http://www.fda.gov/cder/pediatric/S-650-PREA.pdf [Accessed 2008 May 26]
68. US Food and Drug Administration. Guidance for industry: how to comply with the pediatric research equity act [online]. Available from URL: http://www.fda.gov/cder/guidance/6215dft.pdf [Accessed 2008 May 26]
69. US Food and Drug Administration, Department of Health and Human Services. 21 CFR Parts 201, 312, 314 and 601. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients: final rule [online]. Available from URL: http://www.fda.gov/ohrms/dockets/98fr/120298c.pdf [Accessed 2008 May 26]
70. Foley Hoag LLP. Overview of the Food and Drug Administration amendments act of 2007. Life Sciences Alert 2007 Sep 21 [online]. Available from URL: http://www.foleyhoag.com/~/media/Files/Publications/Alerts/Life%20Sciences/LifeSciences_Gvt_Strategies_Alert_092107.ashx [Accessed 2008 May 26]
71. US Food and Drug Administration. Drugs to which FDA has granted pediatric exclusivity for pediatric studies under section 505A of the Federal Food, Drug, and Cosmetic Act [online]. Available from URL: http://www.fda.gov/cder/pediatric/exgrant.htm [Accessed 2008 May 26]
72. Pasquali SK, Sanders SP, Li JS. Oral antihypertensive trial design and analysis under the pediatric exclusivity provision. Am Heart J 2002; 144 (4): 608-14
73. US Food and Drug Administration, Division of Metabolic and Endocrine Drug Products. sNDA application for Fosamax (alendronate sodium) [online]. Available from URL: http://www.fda.gov/cder/foi/esum/2003/20560se1-038BP-CA.pdf [Accessed 2008 Jun 3]
74. Birenbaum L. Labeled products with significant new information [online]. Available from URL: http://www.fda.gov/cder/pediatric/presentation/dlb2-DIA-Mar2003/sld011.htm [Accessed 2008 Jun 3]
75. Boston BA, Drury Brown MK. McCune-Albright syndrome. eMedicine [online]. Available from URL: http://www.emedicine.com/ped/topic1386.htm [Accessed 2008 Jun 3]
76. US Food and Drug Administration. Approved active moieties to which FDA has issued a Written Request for Pediatric Studies under Section 505A of the Federal Food, Drug, and Cosmetic Act [online]. Available from URL: http://www.fda.gov/cder/pediatric/wrlist.htm [Accessed 2008 Jun 3]
77. Clinical trials in children, for children [editorial]. Lancet 2006 Jun 17; 367 (9527): 1953
78. European Medicines Agency. The European paediatric initiative: history of the paediatric regulation. EMEA/17967/04 Rev 1 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/paediatrics/1796704en.pdf [Accessed 2008 Jun 3]
79. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Off J EU 2006 Dec 27 [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf [Accessed 2008 Jun 3]
80. Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf [Accessed 2008 Jun 3]
81. Wikipedia. Supplementary protection certificate [online]. Available from URL: http://en.wikipedia.org/wiki/Supplementary_protection_certificate [Accessed 2008 Jun 3]
82. EMEA. Paediatric Committee [online]. Available from URL: http://www.emea.europa.eu/htms/human/paediatrics/pdco.htm [Accessed 2008 Jun 3]
83. EMEA. EMEA Paediatric Working Party meets for last time ahead of creation of new Paediatric Committee [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/press/pr/25919207en.pdf [Accessed 2008 Jun 3]
84. EMEA. New Paediatric Committee holds its first meeting [press release; online]. Available from URL: http://www.emea.europa.eu/pdfs/human/pdco/29568907en.pdf [Accessed 2008 Jun 3]
85. Seigneuret N. Implementation on the paediatric regulation EMEA views: 2007 EMEA – EFPIA info day [online]. Available from URL: http://www.emea.europa.eu/pdfs/conferenceflyers/EMEA-EFPIA_2Feb2007/1330-N_Seigneuret.pdf [Accessed 2008 Jun 3]
86. EMEA. Practical aspects on how to submit an application for paediatric investigation plan and requests for waiver and deferral. EMEA/252191/2007-rev 5

[online]. Available from URL: http://www.emea.europa.eu/pdfs/human/paediatrics/practical_aspects.pdf [Accessed 2008 Jun 3]
87. EMEA. Paediatric investigation plans (PIPs), waivers and modifications [online]. Available from URL: http://www.emea.europa.eu/htms/human/paediatrics/pips.htm [Accessed 2008 Jun 3]
88. EMEA. Submission of paediatric studies [online]. Available from URL: http://www.emea.europa.eu/htms/human/paediatrics/studies.htm [Accessed 2008 Jun 3]
89. EMEA. Compliance [online]. Available from URL: http://www.emea.europa.eu/htms/human/paediatrics/compliance.htm [Accessed 2008 Jun 3]
90. EMEA. Scientific advice [online]. Available from URL: http://www.emea.europa.eu/htms/human/paediatrics/sci_advice.htm [Accessed 2008 Jun 3]
91. EMEA. Scientific advice and protocol assistance [online]. Available from URL: http://www.emea.europa.eu/htms/human/sciadvice/Scientific.htm [Accessed 2008 Jun 3]
92. Committee for Medicinal Products for Human Use. Guideline on conduct of pharmacovigilance for medicines used by the paediatric population. EMEA/CHMP/PhVWP/235910/2005, rev 1 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/phvwp/23591005en.pdf [Accessed 2008 Jun 3]
93. EMEA. Paediatric-use marketing authorisations (PUMAs) [online]. Available from URL: http://www.emea.europa.eu/htms/human/paediatrics/pumas.htm [Accessed 2008 Jun 3]
94. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf [Accessed 2008 Jun 3]
95. US Food and Drug Administration. Overview of new legislation: Food and Drug Administration Amendments Act of September 2007Amendments 2007 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4344s1_10_01_Introduction%20Murphy.pdf [Accessed 2008 Jun 3]
96. EMEA. Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/draft_guideline_pip_2007-02.pdf [Accessed 2008 Jun 3]
97. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_83/dir_2001_83_en.pdf [Accessed 2008 Jun 3]
98. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the community code relating to medicinal products for human use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_63/dir_ 2003_63_en.pdf [Accessed 2008 Jun 3]
99. EMEA. EMEA decisions on paediatric investigation plans (PIPs), including deferrals and waivers, and on modification of an agreed PIP [online]. Available from URL: http://www.emea.europa.eu/htms/human/paediatrics/decisions.htm [Accessed 2008 Jun 3]
100. Wikipedia. Gaucher's disease [online]. Available from URL: http://en.wikipedia.org/wiki/Gaucher%27s_disease [Accessed 2008 Jun 3]
101. Mehta A, Hughes DA. Fabry disease. GeneReviews [online]. Available from URL: http://www.genetests.org/query?dz=fabry [Accessed 2008 Jun 3]
102. Aggarwal S. What's fueling the biotech engine? Nature Biotechnol 2007; 25: 1097-104 [online]. Available from URL: http://www.nature.com/nbt/journal/v25/n10/abs/nbt1007-1097.html [Accessed 2008 Jun 3]
103. Cystic Fibrosis Foundation. About cystic fibrosis: what you need to know [online]. Available from URL: http://www.cff.org/AboutCF/ [Accessed 2008 Jun 3]
104. Pediatric exclusivity labeling changes as of May 1, 2008 [online]. Available from URL: http://www.fda.gov/cder/pediatric/labelchange.htm [Accessed 2008 Jun 3]
105. Department of Health and Human Services. The Orphan Drug Act: implementation and impact [online]. Available from URL: http://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf [Accessed 2008 Jun 3]
106. EU. Fighting rare diseases: 22 new orphan drugs in five years [press release; online]. Available from URL: http://europa.eu/rapid/pressReleasesAction.do?reference=IP/06/844&type=HTML&aged=0&language=EN&guiLanguage=en [Accessed 2008 Jun 3]
107. Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 5th ed. Philadelphia (PA): Lippincott Williams & Wilkins, 2006
108. Hirschfeld S, Ho PTC, Smith M, et al. Regulatory approvals of pediatric oncology drugs: previous experience and new initiatives. J Clin Oncol 2003; 21: 1066-73
109. Cancer Research UK. Childhood cancer survival statistics [online]. Available from URL: http://info.cancerresearchuk.org/cancerstats/childhoodcancer/survival/ [Accessed 2008 Jul 14]
110. Ries LAG, Smith MA, Gurney JG, et al., editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda (MD): National Cancer Institute, 1999. NIH Pub. No. 99-4649 [online]. Available from URL: http://seer.cancer.gov/publications/childhood/ [Accessed 2008 Jun 3]
111. Center for Drug Evaluation and Research. Pediatric cancer therapeutics: letter of interest [online]. Available from URL: http://www.fda.gov/cder/pediatric/pedcancerletter.htm [Accessed 2008 Jun 3]
112. National Cancer Institute. Targeted cancer therapies: questions and answers [online]. Available from URL: http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted [Accessed 2008 Jun 3]
113. Smith M. Evolving molecularly targeted therapies and biotherapeuics. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. 5th ed. Philadelphia (PA): Lippincott Williams & Wilkins, 2006: 366-404
114. EMEA. Note for guidance on evaluation of anticancer medicinal products in man: addendum on paediatric oncology. EMEA/CPMP/EWP/569/02 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/ewp/056902en.pdf [Accessed 2008 Jun 3]
115. EMEA. Note for guidance on evaluation of anticancer medicinal products in man. CPMP/EWP/205/95 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/ewp/020595en.pdf [Accessed 2008 Jun 3]
116. Innovative Therapies for Children with Cancer: European Consortium [online]. Available from URL: http://www.itcc-consortium.org/ [Accessed 2008 Jun 3]
117. SIOP Europe – the European Society for Paediatric Oncology [online]. Available from URL: http://www.ecco-org.eu/About-Ecco/Membership/SIOP-Europe/page.aspx/331 [Accessed 2008 Jun 4]
118. Houghton PJ, Morton CL, Tucker C, et al. The pediatric preclinical testing program: description of models and early testing results. Pediatr Blood Cancer 2006; 49 (7): 928-40 [online]. Available from URL: http://www3.interscience.wiley.com/journal/113441320/abstract [Accessed 2008 Jun 3]
119. National Cancer Institute. Childhood cancer resources: pediatric clinical trials cooperative groups and consortia [online]. Available from URL: http://ctep.cancer.gov/resources/child.html [Accessed 2008 Jun 3]
120. Children's Oncology Group (COG) [online]. Available from URL: http://www.childrensoncologygroup.org/ [Accessed 2008 Jun 3]
121. EMEA/CHMP. Guideline on clinical trials in small populations. CHMP/EWP/83561/2005 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/ewp/8356105en.pdf [Accessed 2008 Jun 3]
122. EMEA. Orphan drugs and rare diseases at a glance. EMEA/290072/2007 [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/comp/29007207en.pdf [Accessed 2008 Jun 3]
123. National Institutes of Health. Request for proposals for clinical trials: NICHD's approach to the study of off-patent drugs mandated by the BPCA [online]. Available from URL: http://bpca.nichd.nih.gov/clinical/rfp/index.cfm [Accessed 2008 Jun 3]
124. Seventh research framework programme (FP7) [online]. Available from URL: http://cordis.europa.eu/fp7/home_en.html [Accessed 2008 Jun 3]
125. Medicines for Children Research Network [online]. Available from URL: http://www.mcrn.org.uk/ [Accessed 2008 Jun 4]
126. Medicines for Children Research Network [online]. Available from URL: http://www.mcrn.nl/ [Accessed 2008 Jun 4]
127. PAED-Net: a German paediatric network [online]. Available from URL: http://www.paed-net.org/ [Accessed 2008 Jun 4]
128. Finnish Investigators Network for Pediatric Medicines – FINPEDMED [online]. Available from URL: http://www.hyksinstituutti.fi/document.asp?intSiteID=2&intDocID=350 [Accessed 2008 Jul 14]

129. RIPPS; le Reseau d'Investigations Pédiatriques des Produits de Santé [online]. Available from URL: http://site8.actengo.com/ripps/site/defaut/ [Accessed 2008 Jul 14]
130. Pediatric Rheumatology International Trials Organisation (PRINTO) [online]. Available from URL: http://www.printo.it [Accessed 2008 Jun 4]
131. PENTA [online]. Available from URL: http://www.pentatrials.org/ [Accessed 2008 Jul 14]
132. Task-force in Europe for Drug Development for the Young. [online]. Available from URL: http://www.teddyoung.org [Accessed 2008 May 25]
133. European Medicines Agency. The Network of paediatric networks at the EMEA: draft implementing strategy (for public consultation until 20th August 2007) [online]. Available from URL: http://www.emea.europa.eu/pdfs/human/paediatrics/29559407en.pdf [Accessed 2008 May 25]
134. World Health Organization. Make medicines child size [online]. Available from URL: http://www.who.int/childmedicines/en/ [Accessed 2008 May 25]
135. Lamprill J, Fowler T. Consent and assent in paediatric clinical trials. In: Rose K, van den Anker JN, editors. Guide to paediatric clinical research. Basel: Karger, 2007

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