

Original paper

Regulation and paediatric drug trials: patents, plans, and perverse incentives

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The facilitation of tight regulatory frameworks necessary to ensure that new drugs are safe and effective have yet to be effectively applied within the paediatric population. Utilization of unlicensed and off-label drugs in children results in a variety of problems ranging from inefficacy, adverse reactions and in some cases death. This ethically questionable behaviour has led the European government to legally force pharmaceutical companies to propose paediatric applications and carry out clinical studies at early stages of drug development. The new European Paediatric Regulation implemented in 2007 opens a new era of paediatric drug development and will offer the opportunity to vastly improve children's health. However, this brighter outlook for the paediatric community might encourage potentially unethical behaviour in a pharmaceutical industry that finds itself in economically unstable times.

The article records the gradual evolution of the US Paediatric Exclusivity Plan and the underlying principle of the newly introduced European Paediatric Regulation. It discusses some of the potential drawbacks and detrimental consequences of implementing the new European regulation, and the prospects of avoiding these by critically evaluating the difficulties experienced by the US.

Keywords: *unlicensed/off label drug use, children, US Paediatric Exclusivity Plan, European Paediatric Regulation, Paediatric Investigation Plan, requirements, incentives, patents, developing/transition countries, exploitation, cost-effectiveness, publication bias*

Introduction

New medicines are now highly regulated in the UK through The Medicines for Human Use (Clinical Trials) Regulations 2004. They superseded The Medicines Act 1968 in ensuring that all legalized drugs are safe, effective and of a high quality safeguarding the recipient [1]. Legislation on new drugs in the USA followed public outcry over the 1937 Elixir Sulfanilamide

tragedy, in which over 100 children died after using a drug formulated with a toxic, untested solvent. In the UK, legislation followed the thalidomide disaster in the 1960s which again afflicted children. However, current rules concerning the conduct of clinical trials and authorization of new medicines fail to protect children equally well by facilitating the use of unlicensed/off-label medicinal products in

paediatrics and neglecting clinical trials in a paediatric population. Conroy et al and many others reported that numerous drugs used in children are either unlicensed or prescribed off-label outside the terms of the product licence. Up to two thirds of children in hospitals may be taking unlicensed medication, with estimates of around 40% of drugs prescribed have never been tested on children. These figures are more extreme in neonatal intensive care units, where up to 90% of babies are given unlicensed/off-label drugs, far greater than in any other paediatric setting [2-6]. Clinicians are left with no choice but to improvise the administration of numerous drugs by extrapolating data from adult trials and splitting or crushing pills in an attempt to create child sized dosages in palatable form. Such behaviour has been associated with numerous risk of adverse reactions, over-dosing, under-dosing and in some cases even death [6-9]. Concerns over the unsatisfactory situation have been raised as the government has attempted to promote clinically appropriate investigations of drugs in the paediatric population. The US has moved a long way and has managed to successfully implement major changes in US laws, while little progress was seen in Europe as pharmaceutical companies were reluctant to cooperate due to lack of any governmental legislation. Only very recently did the European Paediatric Regulation come into force [10], which will lead to significant changes in landscaping not only in paediatric but also in adult drug development. This paper explores the gradual development of the US laws and their later European counterpart, and evaluates the many pitfalls and risks that lie ahead that need to be anticipated, and what can potentially be learnt from the US.

Extended patents for paediatric drugs

Hubert Humphrey (1911-1978) the Vice President of the United States, once said 'The moral test of government is how it treats those who are in the dawn of life, the children...' Yet it seems that the most vulnerable patients, the

children, are less protected [11]. In 1979 the US Food and Drug Administration (FDA) began to gently persuade the pharmaceutical companies to provide paediatric labelling information based on full clinical trials in children, but little came out of this. Many years down the line in mid 1990s the US congress passed the FDA Modernization Act, of which section 505(A) was the 'Paediatric Exclusivity Provision' [12]. It provided economic incentives in the form of six months of additional patent protection for approved drugs, in return requiring the companies to conduct safety and efficacy studies with children. Although the act itself proved to be very successful in stimulating paediatric trials, it was still heavily commercialized, targeting drugs that increased profit margins rather than areas of greater therapeutic need [13]. The laws have since changed and new laws have been implemented such as the Best Pharmaceuticals for Children Act of 2002 [14] and the Paediatric Research Equity Act of 2003 [15], yet the incentives and obligations still remain in place.

Perverse incentives

It has long been recognized by the pharmaceutical industry that the paediatric market to this day remains very small; hence the consideration of clinical trials in children is highly unattractive. A study carried out by Li et al on the economic return of paediatric clinical trials showed that under the US Paediatric Exclusivity Plan, the pharmaceutical companies showed financial returns that were very close to the original investment in the trial and one product showed negative return on sales. A high rate of return of over a billion was observed with blockbuster drugs, while a much lower rate of return was seen with most other products [16]. The US General Accounting Office has reported that the majority of the products entered into the Paediatric Exclusivity Plan have annual sales of less than \$200 million [17], indicating that these drugs were not among the best selling drugs, resulting in only modest return on investment. Nevertheless, despite the moderate

profit prospective, the US Paediatric Exclusivity Plan has been shown to be very effective, with the industry responding favourably. It has been estimated that up to 80% of the paediatric studies requested by the FDA have been completed, as opposed to the 15% completion rate before the introduction of the plan [18]. This raises questions as to why the pharmaceutical industry would participate in trials that bring them only marginal profits, when the law doesn't force them to do so.

To make paediatric trials more cost-effective, a study published in 2010 [19] showed for the first time that more than a third of the enrolled children in clinical trials were in developing or transition countries, since the Paediatric Exclusivity provision came into place. 174 published studies under the Exclusivity Plan were included from 1998 to 2007, all conducted in response to the written request issued by the FDA. Of these 9% did not reveal any information on the location of the study, of those that did report revealed that 65% of the studies were conducted in one or more countries outside the US, and 11% did not include any studies within the US. Out of the 54 countries represented, they reported that 38% of trials enrolled children in one or more sites located in a developing or transition country. A total of 79 trials that enrolled more than 100 children, of these 87% enrolled patients outside the US. 71% of these trials were sponsored by the larger pharmaceutical companies, of which 73% enrolled children from outside the US. More than a third of the cardiovascular or allergy/immunology trials were also conducted in developing or transition countries [19]. This paper illustrates solid evidence of the true consequences of the US Paediatric Exclusivity Provision, and raises some serious ethical concerns regarding exploitation of children and families in developing nations [20].

Third-world nations eg in Africa offer the possibility of a larger more diverse pool of research subjects, which enables companies to reduce trial and drug development time lines.

There are fewer strict regulatory frameworks, elaborate safety checks and participant compensation requirements, compared to Western countries. And the costs of labour and infrastructure are significantly reduced [20-23]. This raises serious ethical concerns with regards to not only the appropriateness of the study in question, but also whether the particular country will have any direct benefit from these studies. It seems ethical to study diseases that are of high penetrance to these countries such as antimalarial drugs in Africa, but questionable when cardiovascular or rheumatology trials are conducted [24]. It is also unclear as to whether the drugs trialled will become readily available to these countries at affordable prices. Hence, there could be a breach of the Declaration of Helsinki that directly states that every participant enrolled in the trial should, at the end of the trial, have direct access to the proven therapy identified through the clinical trials. Enticement with compensation and medication for trial participation also raises concerns as the families of these children may have annual salaries that are significantly lower than the trial payouts, consequently they view trials as a means of financial gain. It may also be the only way these poor families have access to medical care. The cultural variation of these third-world nations may also be exploited as some expect the child to contribute to the economic stability of their family, and hence bring home the financial incentives they receive from the trials. Furthermore, widespread illiteracy and the overall language barrier makes it easier for companies to circumvent the conventional methods of obtaining fully-informed consent [19-21]. The threat of costly litigation would also be less of a problem as the FDA and other governmental regulators would not be able to provide the same level of subject protection in foreign trials as they are outside their jurisdiction.

Promoting child health?

A study carried out by Benjamin et al for the first time explored the publication status of studies

that were carried out for Paediatric Exclusivity. They showed that out of 253 studies submitted between 1998 and 2004 only 44% of these were published in peer-review journals. They concluded that studies that were completed for paediatric exclusivity are often not published in peer-review journals [25]. The aim of the paediatric exclusivity is to improve the overall health of the paediatric population, yet this task will not be possible if the acquired knowledge from the trials is not well distributed. Peer-reviewed medical literature is the principal route by which practitioners obtain crucial information on the latest updates in therapeutics, and hence can update their knowledge and modify their prescribing behaviours. Their findings concur with previous investigations of publication bias and positive outcome bias [26-28]. The lack of publication of crucial paediatric studies will have devastating consequences on not only the public health risk but also overestimation of efficacy and underestimation of safety of the trialled paediatric drug [27]. Furthermore, unnecessary repetitions of trials may occur if they are not adequately registered in the clinical trial registry with accurate protocols and negative data publication [29]. This poses a major risk to exposing already vulnerable patients to unnecessary trials if negative results were already obtained but not made known to the clinical community.

Plans for paediatrics trials

Not too far behind the US, in 2007 the EU passed Paediatric Regulation (EC) No 1901/2006 into law [30]. The legislation requires that all applications for marketing authorization of new medicinal products must submit a paediatric investigation plan (PIP) to a new Paediatric Committee of the European Medicines Agency. This should contain a full proposal of all the studies needed to support paediatric use and must cover all age groups as well as age-appropriate formulations. The requirement also applies to the addition of new indications, new pharmaceutical form or new route of administration for medicines still covered by the

patent. Following approval a PIP should be undertaken to generate paediatric data, all information being then made public on the EU clinical trials database (EudraCT). This ensures that a plan for paediatric trials is in place after adult pharmacokinetic studies have been conducted and have proved its safety. Following submission of all the information to the regulatory authorities, the medicinal product will be granted an extra six month patent protection through an extension in the duration of its Supplementary Protection Certificate (SPC). Conversely, existing marketing authorization holders can also apply for the PIP to receive the incentives [10,30]. However, paediatric development of drugs already on patent may be extremely slow [31], as companies may be reluctant to submit PIPs for already patented drugs since they are already under pressure to plan paediatric trials when they want to obtain marketing authorization for newly developed drugs. Hence, the attempt to keep the development of paediatric drugs in tandem with the development of new adult drugs will still fall short, as patented drug trials will lag. The regulation also established a new type of marketing authorization called the paediatric use marketing authorization (PUMA), intending to stimulate off-patent drug trials in children [30].

If these are the consequences of utilizing the US Paediatric Provision, that doesn't force the pharmaceutical companies to do paediatric trials, then what does Europe have in store for developing/transition nations? When our law enforces costly paediatric trials with only modest return on investment wouldn't profit driven pharmaceutical companies be trying to carry out these trials in the most cost-effective manner?

Similar perverse incentives?

The financial incentives provided by the government may not be seen as enough to compensate for the additional workload and expertise required for paediatric trials, not to mention the high investment and long duration of time necessary to complete these trials. This

may inevitably lead to far more paediatric trials being carried out in developing or transition nations where the cost and drug development timelines may be slashed, enabling the companies to more readily take advantage of the incentives. These incentives can bring the company up to \$14 billion in profits from the extended patent protection, which can provide a powerful driving force for unethical behaviour [19]. Raising the prices of the paediatric drugs to compensate for the cost of the trials in Europe would be unlikely as a reasonable solution for the pharmaceutical industry as the NHS and insurance plans are unlikely to pay the excess cost when the governments do not restrict the use of off-label or unlicensed drugs in the first place. Even if the NHS does choose to pay for some of these expensive drugs only the minority of the paediatric population would benefit, as they would be strictly selected on the inadequacy/inefficacy of the previous off-label/unlicensed drug formerly used. This is already seen with the adult use of adalimumab, a novel anti-TNF therapy used for autoimmune arthritic conditions, where only a hand full of patients are prescribed the drug on the NHS due to its extremely high cost.

Even though trials in developing nations will provide faster results, can we really expect the knowledge gained from the trials to have sound scientific validity and can we really extrapolate the results accurately? The genetic differences that exist between different populations will likely influence drug effects and may significantly diminish the applicability of results to the target population [32]. Populations in third world nations will undoubtedly have differences in access to health care, baseline disease event rates as well as adherence to therapy; all will inevitably affect treatment effects [24]. Furthermore, the quality of the training and education provided to the investigators, as well as the research infrastructure may also vary considerably resulting in varied results [21]. Taking all these factors into consideration, can we really expect these trials to be as valuable as those carried out in Western countries?

Implications for adult drugs

The introduction of the European Paediatric Regulation that is more stringent than the US regulation may impose a lot of practical and ethical challenges with clinical trials, in particular those revolving around the PIPs. Submission of PIPs may inevitably delay the authorization of new medicinal products for adults, hence in an attempt to improve paediatric health the adult community will be put in jeopardy, in particular when the companies struggle with PIP compliance checks. Such delays are in conflict with their original intent to improve European paediatric medicine without delaying authorization of medicine for adults [10]. Such regulatory framework should not be excessively restrictive as researchers need time to be able to confidently justify their research proposals, rather than avoiding them due to apprehension of criticism at the ethical approval stage, hence a more balanced approach is required.

Implications for small drug companies and drug discovery

Smaller or new pharmaceutical companies may consequently go bankrupt as they may not have the permissive finances or resources to carry out their trials in developing nations. This will drive out any existing competition between the pharmaceutical companies and result in higher cost of drugs. Although it has already become evident that even the larger pharmaceutical companies are beginning to feel the sting of the UK's economic instability. Pfizer one of the world's leading pharmaceutical companies that have a European R&D headquarters at Sandwich in Kent UK is closing down [33]. How are we to expect smaller pharmaceutical companies to survive? It appears that the new European regulations that are intended to bring fast results will lead to a vicious cycle that will only be exacerbated by the UK's failing economy. Although it may prove beneficial for other economically stable European countries, applying force on pharmaceutical industries to provide compulsory paediatric trials will only

drive them out to set up in cheaper locations like China or India, where they will no longer be held by the red tapes of Europe. What fate awaits us then when there will be no one left to do the trials for us at a standard that we would like?

Conclusion

Following the enforcement of the European Regulations a large number of encouraging paediatric trials have been taking place, which have resulted in the improvement of paediatric health. Yet, we must be very cautious that these trials are not only of high quality but are also ethically sound. The study carried out by Pasquali et al has received some criticism of its reliability [34], nevertheless I believe that this research is just in its infancy as it's the first of its kind and will become more evident as more information will become available. If pharmaceutical companies have embraced globalization in adult clinical trials, who are we to say that they won't do the same thing with paediatric trials, especially at a time when the firm hand of the law enforces them to carry out such trials. The pharmaceutical industry has gained quite a reputation for its secrecy; hence it seems quite obvious to state that Pasquali and her colleagues found it challenging to expose the exact locations and proportions of the studies that were carried out outside the US. To prevent the same trend of behaviour from the European regulations we must remain vigilant of where the trials are coming from, and lay down strong ethical and legal foundations to restrict any kind of exploitation, as was observed in the US. This is not a problem that will be solved easily but needs to be considered for years to come, as throwing money at it hasn't proven to be the solution.

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