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REVIEW ARTICLE

The status of paediatric medicines initiatives around the world—what has happened and what has not?

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Abstract
Purpose This review was conducted to examine the current status of paediatric medicines initiatives across the globe.
Methods The authors made a non-systematic descriptive review of current world situation.
Results Two regions, the United States (US) and the European Union (EU), and the World Health Organization (WHO) have introduced strong paediatric initiatives to improve children's health through improving access to better paediatric medicines. The experience from the US initiative indicates that it is possible to stimulate development and study of paediatric medicines and provide important new information for improvement of paediatric therapy. The early results from the EU initiative are similarly encouraging. In Canada, Japan, Australia and other developed countries, specific paediatric medicines initiatives have been less extensive and weaker, with modest results. Disappointingly, current evidence suggests that results from clinical trials outside the US often do not benefit children in the country in which the trials were largely conducted. Pharmaceutical companies that have

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derived a financial benefit commensurate with the cost of doing the paediatric trials in one country do not seem to be making the results of these trials available to all countries if there is no financial incentive to the company. The WHO campaign 'make medicines child size' has produced substantive accomplishments in building improved foundations to improve mechanisms that will enhance children's access to critical medicines in resource-limited settings. However, practically all of this work has been performed using an amalgamation of short-term funding from a variety of sources as opposed to a sustained, programmatic commitment.
Conclusions Although much still needs to be done, it's clear that with concerted efforts and appropriate resources, change is possible but slow. Retaining and fostering public and political interest in paediatric medicines is challenging, but pivotal for success.

Keywords Biomedical research · Legislation · Jurisprudence · Child · Drugs, investigational

Providing children better access to safe and effective medicines addressing their therapeutic needs appeared on the agenda of many countries during the last decade [1]. Pioneering legislation to address paediatric needs came into force in the United States (US) in 1997. The European Union's (EU) Paediatric Regulation and the unanimous adoption by the World Health Assembly of Resolution WHA60.20, 'Better medicines for children', followed in 2007 [2]. The duration these initiatives have been in force may be too short to expect that the problems of some 40 years of children being 'therapeutic orphans' [3] could have been abolished. However, it is long enough to expect some concrete results.

As members of the paediatric clinical pharmacology community representing many countries, our purpose in assembling this review was to examine the current status of paediatric medicines initiatives across the globe, reveal some of the associated challenges/problems and offer some perspective on future needs. We also explore whether the initiatives have spawned any new paediatric medicines initiatives around the world. However, we were not able to report on all developments, or lack of them, addressing paediatric therapeutic needs. For example initiatives addressing the promotion of rational use of medicines (RUM) are beyond the scope of this review. We focus on major initiatives demonstrating commitment of the whole society to narrow the old therapeutic gap between children and adults.

The US and EU legislative/regulatory initiatives

In response to the challenge of improving both the licensing and labelling of drug products for paediatric patients and thereby facilitate access to accurate information and, in some cases, paediatric-friendly drug formulations, both the US and EU have developed significant regulations, the timeframe for which is depicted in Fig. 1. The US regulation has been in force for discrete 5-year periods, with two sunsets, emerging each time with a new name and modifications (Fig. 1). The EU regulation, still in its original form, benefitted during its development from the US experience. In essence, both regulations currently include a requirement part with a reward (on-patent medicines) and a voluntary part with an incentive (off-patent medicines) for paediatric development, both aimed at the pharmaceutical industry. To get the reward or incentive, data from paediatric studies have to be submitted to regulatory authorities for assessment of market authorisation or labelling change. The reward/incentive in both regions is primarily a 6-month extension of patent protection; a provision that, from a fiscal perspective, would appear at the surface to have been of greater benefit for drug manufacturers as opposed to paediatric patients per se [4]. For medicines without intellectual property protection, paediatric development is voluntary. The EU offers an incentive mainly in the form of a 10-year data protection, and in both regions some public funding is available for studies of off-patent medicines. More details on the paediatric initiatives are available from publications and official websites [5–8].

What have the EU and US paediatric regulations already achieved?

The regulatory evolution produced a true renaissance in paediatric clinical pharmacology and drug development in the U.S. As a result of the potential benefit afforded by extended marketing exclusivity, paediatric drug development was given greater emphasis and priority within the pharmaceutical corporate sector. As a result of an expanded number and scope of paediatric drug trials, the quantity and quality of information that could be translated to the labelling of approved drug products markedly increased. For a cohort of 365 trials performed for 153 medicines (December 1997–September 2007), 137 labelling changes resulted, 26% of which included the addition of safety information to improve paediatric medicines use [9]. During the most recent US regulation, the Food and Drug Administration Amendments Act (FDAAA), 305 studies were completed involving over 111,000 paediatric patients between September 2007 and September 2010 (Table 1). By February 2010, paediatric studies permitted over 350 labelling changes, and extended marketing exclusivity was granted for over 170 medicines [10] .

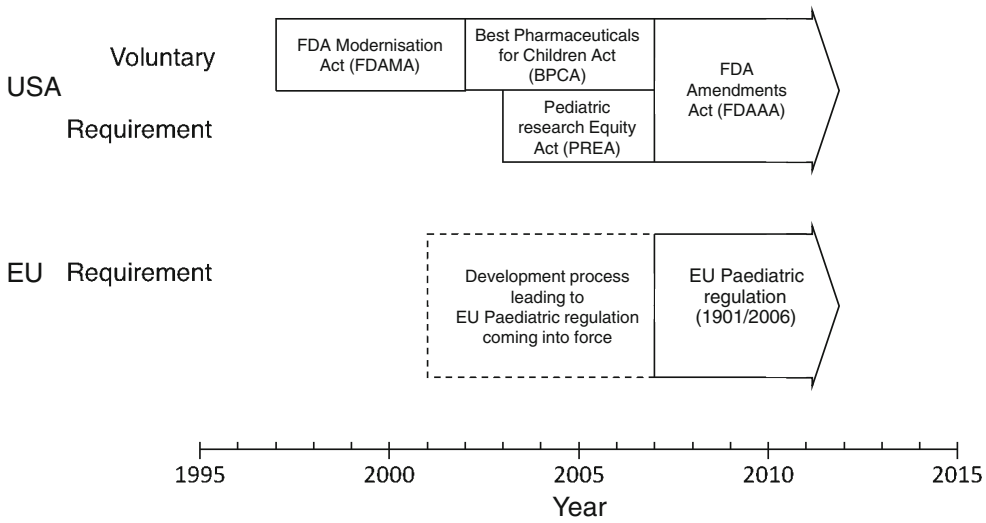

Fig. 1 Timeframe of the US and EU paediatric regulations

The incentive of extended marketing exclusivity of a medicinal product for all approved indications (i.e. both adult and paediatric) has leveraged resources dedicated to the support of paediatric clinical trials in the private (corporate) sector. Data from studies of nine antihypertensive medicines submitted to the FDA from 1994 to 2004 show an average ratio of net economic return to cost (of performing required studies) of 17 (range 4–64.7) [11]. Such rates of return have made it economically feasible for pharmaceutical companies to dedicate resources to paediatric medicines development of products whose paediatric market place could be extremely small (e.g. antihypertensive drugs).

To date, more than 450 of 1,000 applications submitted for a Paediatric Investigation Plan (PIP; the regulatory 'tool' in the EU) or Waiver have received a positive opinion from the Paediatric Committee (PDCO) of the EMA [12]. About one-third related to product-specific waivers (the medicine does not need to be studied in children, e.g. no paediatric indication) [13], and two-thirds concerned a PIP. In contrast, as of January 2010, the proportion of paediatric trials as a percentage of all clinical trials in Europe has increased only moderately (from 8.2 to 9.4% of all trials), reflecting the fact that paediatric trials requested by EMA are generally deferred (82%) years until after adult development [14]. So far, the new European regulation has resulted in only three medicines for which a market authorisation extension of 6 months was granted (losartan, caspofungin, anastrozole). No Paediatric Use Marketing Authorisation (PUMA), the incentive for off-patent medicines, has yet been authorised.

Table 1 Breakdown of Food and Drug Administration Amendments Act (FDAAA) paediatric studies completed between 27 September 2007 and 30 September 2010 [10]

Type of study	BPCA	BPCA + PREA	PREA	Total
Efficacy/safety	28	28	146	202
PK/safety	6	29	11	46
PK/PD	10	8	3	21
Safety	3	3	19	25
Other	0	0	11	11
Total	47	68	190	305

BPCA Better Pharmaceuticals for Children Act, *PREA* Pediatric Research Equity Act

Paediatric regulations in other countries

During the last decade, the US and EU paediatric initiatives and the problems of children's access to appropriate medicines have received wide exposure in professional journals and public media all around the world. In addition, the process leading to the WHA Resolution 60.20, endorsed by almost all governments of the world, also exposed policy makers to these problems. So have other governments followed the WHA resolution and taken steps to develop their own paediatric regulations, or are they just waiting for the US and EU to solve the problems?

Australia, Japan and Canada

If we look at legislative and regulatory reforms, development in Australia, Canada and Japan has been at best modest (Table 2). In Canada, there is a current provision in the Canadian Food and Drug Regulations that provides for a 6-month extension for data protection to innovator companies providing evidence to support a label indication for a product which has value in treating the paediatric age group.

In Japan, there is no comprehensive legislation to provide incentives and mandate development of paediatric

Table 2 Current status of legislative/regulatory paediatric initiatives in some key high-income countries/economic areas around the world

Type of legislation	USA	EU	Japan	Canada	Australia
Legislation to provide incentive for study/development of medicines for children	In effect from 1997	In effect from 2007	Premium (higher price) for new (patent protected) medicines developed for children and for existing ones eliminating unapproved/off-label indications (2006–)	Regulation provides 6 month extension to 8 years of market exclusivity through data protection to innovator companies who provide evidence to support a label indication for a product which has value in treating the paediatric age group (2006–)	No
Legislation requiring study/development of medicines for children	In effect from 2003	In effect from 2007	No	No	No
Other legislative/regulatory measures to increase children's access to existing medicines	Creation of the FDA Office of Pediatric Therapeutics (1998)	Free scientific advice available from regulatory authorities	Government Study Group/Expert Panel on paediatric unlicensed and off-label medicines (established 2005, reorganised 2009)	No	Government Paediatric Medicines Advisory Group to provide advice on paediatric medicines needs/access, within existing legislative and regulatory frameworks (2007–)

medicines [15]. In contrast to the US and EU, Japan has a low penetration rate of generics, therefore extended patent protection for innovator companies may not be an effective option. The voluntary approaches tried, e.g. paediatric premium and extension of re-examination period, turned out not to be effective incentives [16]. In 2010, the price premium for promotion of new medicines creation and resolution of unapproved/off-label medicines was introduced as part of the new drug development promotion scheme. With this scheme, industries must comply with the request from the Ministry of Health, Labour and Welfare (MHLW)/the Study Group on Unapproved and Off-label Drugs of High Medical Need to get the premium for all their new innovative medicines. Development of 60 unapproved medicines and 122 off-label indications has been requested by the MHLW as of February 2011.

In Australia, paediatric-specific medicines initiatives have been proposed through professional and government advisory bodies since the mid-1990s. These address improvements in paediatric medicines research, regulation and public subsidy to improve children's access to appropriate medicines, coupled with systematic strategies to support quality use of medicines (QUM), a cornerstone of Australia's comprehensive National Medicines Policy (NMP) [17, 18]. Despite many years of advocacy and awareness of recent international initiatives, Australia still lacks any legislative and regulatory reforms addressing paediatric medicines. Although other initiatives in recent years have led to some improvements in children's access to needed medicines through public subsidy [19], there is as yet no explicit whole-of-government commitment to give high priority to children's medicines issues, with ongoing major gaps in needed initiatives (Tables 2 and 3) and lack of a well coordinated and resourced national strategy [18]. Strong professional advocacy is continuing on multiple fronts.

Other countries

The Korean Food and Drug Administration set up a task force team on off-label medicine use evaluation in April 2010. We are not aware of any other significant legislative or regulatory initiatives of the types described earlier in other developed countries of the world.

In middle and low income countries, effort needs to first be devoted to build or improve the legislative and regulatory framework necessary for regulatory oversight of paediatric clinical trials and regulatory assessment of paediatric medicines. The types of paediatric initiatives as described for some of the rich countries are otherwise not possible, children's access to medicines is compromised and risk of exploitation in clinical trials remains high [20].

In Latin America, regulatory agencies have embarked on the crucial effort to harmonize procedures and adhere to

Table 3 Current status of paediatric initiatives to help paediatric medicines research in some key high-income countries/economic areas around the world

Type of initiative	USA	EU	Japan	Canada	Australia
Dedicated funding for research/development of paediatric medicines	Primarily available through various institutes comprising the National Institutes of Health	EU (EU Framework Program), joint national (ERA-NET PRIOMEDCHILD 2010) and some national (the Netherlands 2009–2017)	No	No	No
National (regional) network to increase capacity for study of paediatric medicines	Pediatric Pharmacology Research Unit (PPRU) Network, 1994–2010; Clinical Translational Science Award (CTSA) Pediatric Pharmacology Consortium, 2008–2010 and NIH Pediatric Trial Network (PTN), 2010-2017	European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) consisting currently of 17 existing national and European networks and centres with specific expertise in performing studies in children (2011-)	Pediatric Clinical Trial Network is being established as a part of the activity of Japanese Association of Children's Hospitals and Related Institutions (JaCHRI)	No	No
Training/capacity building initiatives in the area of paediatric medicines research	National Institute of Child Health and Human Development (NICHD) support of individual fellows (1998–2010); supplementation of existing adult clinical pharmacology training programs (T32) and creation of two training programs (T32) dedicated to paediatric clinical pharmacology (2011)	Global Research in Paediatrics (GRIP), a Network of Excellence project funded by EU 7th Framework Program for 2011–2015 has about 40% of resources dedicated for training/capacity building internationally	Occasional short courses on paediatric clinical research funded by government grants	No	No

good clinical practice (GCP) guidelines. These initiatives [21] have led to the approval of a specific guideline for clinical trials in the paediatric population [22, 23], currently under discussion by individual member countries [24]. For developing regulatory capacity to handle paediatric medicines globally, the Paediatric Medicines Regulator's Network (PmRN) was recently set up by the WHO with representatives from national medicines regulatory authorities (NMRAs) from all regions, as part of the WHO's Better Medicines for Children initiative.

The WHO Better Medicines for Children initiative

The WHA60.20 Resolution 'Better Medicines for Children' adopted in May 2007 urges WHO Member States and the WHO to undertake many activities, such as improving paediatric medicines research, regulation, access and rational use [1, 2]. Early achievements have been impressive, particularly in view of the fact that the Member States did not provide any funding for the work. Progress has largely been possible due to a US$9.7 million grant from the Gates Foundation to WHO and UNICEF in 2009. WHO has been spearheading a global campaign launched in December 2007, 'Make Medicines Child Size', to reach the Better Medicines for Children resolution's goals, with an extensive list of the achievements to date [25].

The first, and probably most important, achievement has been the establishment of a Model List of Essential Medicines for Children (EMLc) [26, 27]. The Third EMLc has recently been adopted. Considering the importance of the WHO Essential Medicines concept to medicines access in resource-limited settings [28, 29], the significance of the EMLc should not be underestimated. WHO has also followed up with a Model Formulary for Children [30].

The majority of WHO's other achievements [25, 31] lay foundations for more concrete actions to follow, but some may develop to new international paradigms. These include work to develop the best method to estimate body weight easily and reliably for correct dosing for paediatric patients, and the suggested shift from liquid to flexible solid oral dosage forms as priority paediatric formulations [32].

At the country level, early results of this resolution have been seen in some African and Asian countries. In Sri Lanka, paediatric formulations and essential medicines for children have been included in the last two revisions of the National Essential Medicines [33, 34]. In India, the Indian Academy of Paediatrics has prepared an EMLc. Some

states in India have included paediatric formulations into their EML while others are in the process of doing so (personal communication).

Strengthening infrastructure and building capacity for research and development of paediatric medicines

Providing children with better medicines will require significantly more paediatric medicines research. This will require development of infrastructure, capacity building and funding. The US and EU paediatric initiatives are establishing new networks and expanding existing networks with specific expertise in performing paediatric clinical trials and providing dedicated funding for research and training (Table 3).

In anticipation of the need to create an integrated clinical trial platform to embrace the opportunities in paediatric drug development afforded by changes in regulations (Fig. 1), the US National Institutes of Health, through its Institute of Child Health and Human Development (NICHD), created the Pediatric Pharmacology Research Unit (PPRU) Network. Based on the performance of the PPRU Network (e.g. over 160 clinical trials, approximately 70% of which were sponsored by a pharmaceutical company and over 70% of which constituted a phase I or II study; unpublished data obtained from the PPRU Network Operations Center, September 2010), it could be argued that this model was successful as an early phase clinical trial platform.

To facilitate and support this transition in research focus and avoid duplication with efforts on behalf of the pharmaceutical industry, the NIH has refined its approach to facilitate paediatric clinical drug trials [35]. A NICHD-funded Pediatric Trial Network (PTN) has recently been created with a commitment of US$95 million over the next 7 years. The PTN [36] will focus primarily on the study of off-patent medicines prioritized as part of the provisions of BPCA. NICHD anticipates the need to initiate activities in approximately five to ten therapeutic areas, with multiple approaches for each therapeutic area. Much of the work of the PTN over the next 7 years will be done in collaboration with the FDA.

In Europe, creation of a European network [European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)] of existing national and European networks and centres with specific expertise in performing studies in children was one of the obligations given to the EMA by the Paediatric Regulation [37, 38]. Launched in March 2011 Enpr-EMA aims to foster high-quality ethical research on medicines for use in children through networking and stakeholder collaboration with members from both within and outside the European Union. It remains to be seen what will come out of the Enpr-EMA and when. However, EMA will not be funding the networks in any way. The 17 member networks have been established with mostly national grants and funding from public or private sources, including in some cases support from the pharmaceutical industry. Multinational speciality networks, such as the Paediatric European Network for the Treatment of AIDS (PENTA) and the Pediatric Rheumatology International Trials Organisation (PRINTO), have been successful in creating models for financing their infrastructure. The newer multi-speciality national networks have in many cases already run into problems, with an exception of the UK-MCRN, which receives considerable government support. After the national external support for establishment of some networks decreased or ceased, they have not, as expected, been able to rely on income from performing sponsored clinical trials from PIPs because these have included deferrals, and the real increase of paediatric trials is still to come [14].

The Canadian Institutes for Health Research (CIHR) has hosted a Drug Safety and Effectiveness Network, and—while not specifically mandated for research exclusively in maternal-child health—has recently awarded eight competitive research awards for applications focused on drug safety or effectiveness in reproductive or paediatric research topics. Canada also has a national research network, the Maternal, Infant, Child and Youth Research Network (MICYRN) [39], founded in 2006 as a collaborative network of 17 participating child/child-maternal academic health centres. Although not a paediatric clinical pharmacology or paediatric clinical trials network per se, the over 120 research networks of MICYRN formed by investigators working in the same specialty, on diseases, or populations have over 450 paediatric clinical trials recruiting at sites in Canada, which places Canada very high in national performance across the world. MICYRN is also participating in the European Enpr-EMA network.

In Japan, the Japanese Association of Children's Hospitals and Related Institutions (JaCHRI) established a paediatric clinical trial network in collaboration with other subspecialty networks. The National Center for Child Health and Development (NCCHD) is getting funding from the MHLW for the infrastructure and education for this JaCHRI clinical trial network.

In Australia a number of centres and national networks are involved in paediatric clinical trials and clinical research generally, supported by funding from a variety of sources. Unlike many other national research councils, the Australian National Health and Medical Research Council (NHMRC) does not have an explicit focus for paediatric and child health research. Despite wide professional support and many years of strong advocacy by various stakeholders for dedicated resources, national infrastructure

and capacity building specifically for paediatric medicines research, currently Australia still lacks these (Table 3). Although encouraging recent developments in national capacity building for clinical trials [40] are anticipated to also support paediatric clinical trials and medicines research, the lack of explicit policy commitments and accompanying funding continues to pose major barriers to significant progress.

Enrolling children in clinical trials is common in Latin America [41, 42], but most are run by international pharmaceutical corporations [42]. Investigator-initiated paediatric trials are less common in part due to significant costs and regulatory obstacles faced by independent investigators. Funding is limited and mostly for specific topics such as neglected diseases and common paediatric disorders, and rarely aimed at the development of medicines for children. A few agencies [e.g. TDR/WHO, Drugs for Neglected Diseases initiative (DNDi)] provide funds specifically for the development of paediatric medicines, but that are also restricted to specific areas such as neglected or emerging diseases [43, 44]. Some agencies (e.g. DNDi) provide funds specifically for the development of paediatric medicines.

India is well known for its strong generic pharmaceutical industry, which supplies generic medicines (including those for paediatric patients) throughout the developing world. Paediatric clinical trials for medicines intended to be marketed in more developed countries are to some extent conducted in India. The Clinical Trial Registry of India has registered 81 clinical trials in children from 2006 till 15 August 2010 [45]. In India, the WHO has dedicated funds for research, development of paediatric medicines and capacity building including building a national network. In South-Asia, as in other parts of the developing world, the funding priority is to provide access to paediatric medicines, and research is more focused on providing data on availability and use of paediatric medicines than on paediatric clinical trials. Not surprisingly, the major limitation in carrying out research is the lack of dedicated funding required to support it.

Will the countries without a strong paediatric initiative benefit from the initiatives elsewhere?

Disappointingly, evidence from Europe before the paediatric regulation [46], and from Australia and New Zealand [47] and Canada (unpublished) does not support the contention that children from developed countries without a strong financial reward have benefitted to any significant extent from the US initiative, at least in the form of an increase in paediatric labelling or availability of paediatric formulations. International companies do not appear to be willing to voluntarily submit data collected in the US to support the authorisation of paediatric indications elsewhere. This is particularly disturbing when considering that 65% of the published studies conducted in 1998–2007 under the US regulations were conducted in at least one country outside the US, and 11% did not include any sites in the US [42].

The evidence seems clear; we live in a hostage environment. Countries without strong incentives/rewards for submission of paediatric data are unlikely to benefit in the form of increased paediatric labelling, even when the cost of the studies has already been covered by financial rewards from the US or EU, and despite the paediatric population of the country having contributed to these studies. In fact such countries, even rich ones such as Canada and Australia, run the risk of their paediatric population being exploited for the incentives available elsewhere.

Will the initiatives provide children access to the medicines they need?

The studies done so far, with the majority of data from the US, have resulted in improved understanding of the pharmacokinetics of medicines prescribed for children, important changes in dosing and in safety information [9, 48]. While all of the medicines/formulations studied under the US initiatives ostensibly had some demonstrable paediatric use, the fiscal attractiveness of 6 months of market exclusivity resulted in the study of many medicines within a given class that are widely used in infants and children (e.g. the proton pump inhibitors) and in some instances, specific medicines with extremely low paediatric use (e.g. alendronate, anagrelide, dorzolamide) [49]. In contrast, many very widely used and important paediatric medicines without patent life left remain to be sufficiently studied (e.g., clindamycin, fluconazole, metronidazole).

None of the medicines with market authorisation extension in Europe targets a major paediatric disease. The PIPs received by the EMA mainly concern medicines targeting adult diseases, which is in line with economic profit expected by companies [14]. For example, of 29 anticancer medicines authorised since 2007, only 6 have a full paediatric indication [50]. Usually a waiver in oncology is issued based on the histological type of disease, not based on a medicine's mechanism of action. However, the same medicines that may be effective in adult cancers also have the potential to benefit children with cancer. Of all PIPs approved, only 26 and 35% of medicines need to be studied in young infants and neonates respectively. As the major changes in PK are expected in the first 2 years of life, it is surprising, and also disappointing, that many medicines are still not studied in the most vulnerable population [13].

However, the initiatives have many additional beneficial effects. As a direct result of the increased activity in paediatric clinical trials over the last decade, development of high quality approaches for the study of medicines has dramatically increased the quality and quantity of knowledge generated (e.g. developmental differences in drug disposition and action and their effect on the dose-concentration-effect relationship; occurrence of age-specific adverse effects). The incorporation of new technologies such as pharmacogenomics into the context of a regulatory paediatric drug trial has enhanced our ability to study increasing biological complexity associated with ontogeny and disease and to use this information to transition paediatric therapeutics from a predominantly medicine-based orientation to a patient-based orientation (i.e. personalized medicine) [51]. The published data on efficacy and safety of medicines becoming available also have the potential to benefit national programs for rational use of medicines in the paediatric population worldwide.

A major benefit for children globally is illustrated by the improved access of children to HIV/AIDS medicines in resource-limited settings. For adults in developing countries the potential to access ARVs significantly improved when pharmaceutical companies in developing countries began to produce generic medicines at vastly reduced prices after 2001. For children, the reduced drug costs unmasked lack of appropriate paediatric formulations as a key impediment [52]. Increased international support and funding resulted in research evidence that use of generic adult fixed drug combinations could provide an interim solution for scaling up of ARV treatment in children [53, 54]. As a result the proportion of children in need of ARVs in low- and middle-income countries who received them rose from 7% in 2005 to 29% at the end of 2009 (2009 adult coverage was 36%) [55]. Although much more needs to be done, these developments indicate that change is possible. However, it is also clear that even modest improvements take decades not years to achieve.

Conclusions

Currently only two regions, the US and EU, have strong paediatric initiatives containing both incentives and requirements for the development and regulatory assessment of paediatric medicines. These initiatives express a strong commitment by governments and the whole society of these regions for change. The US experience to date shows that it is possible to stimulate development and study of paediatric medicines and provide important scientific data for improvement of paediatric therapy, albeit not yet optimally aligned with priority child health needs. Clearly the incentives work better for new medicines still under patent protection. In contrast, for off-patent medicines additional measures such as dedicated public funding are needed. The weaker paediatric initiatives some countries have tried have not been successful and indicate that broad societal commitment to change is still missing in many regions. So far it also seems that countries without strong paediatric initiatives have not benefitted substantially from developments elsewhere. Underdeveloped legal and regulatory frameworks and the weak economy of middle to low-income countries makes the types of paediatric initiatives discussed here unreachable. Although some indirect benefits have been noted in such countries, available evidence also indicates a clear risk of exploitation of their paediatric population for clinical trials performed for countries with strong initiatives.

The WHO Better Medicines for Children initiative has done a substantial amount of work in building and improving the foundations for children's access to critical medicines in resource-limited settings. However, practically all of the WHO work has been performed using an amalgamation of short-term funding from a variety of sources as opposed to a sustained, programmatic commitment.

Even in the best possible scenario it is likely to take decades for the current paediatric initiatives to significantly narrow the gap between paediatric and adult populations in availability and access to medicines of comparable quality, efficacy and safety. Although much still needs to be done, developments to date indicate that with concerted efforts and appropriate resources, change is possible but slow. One of the biggest challenges is how to retain and foster further development of public and political interest in paediatric medicines in existing and new regions, which is pivotal for longer term funding and ultimate success of these initiatives globally. Achieving well coordinated, well resourced and focused national strategies for paediatric medicines research, regulation, access and rational use will require strong and sustained advocacy on multiple fronts highlighting these needs as priorities for all regions of the world.

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