The Globalization of Pediatric Clinical Trials

**AUTHORS:** Julia Dunne, MD,a,b M. Dianne Murphy, MD,a and William J. Rodríguez, MD, PhD

aOffice of Pediatric Therapeutics, Office of the Commissioner, US Food and Drug Administration, Silver Spring, Maryland; and bSpecial Populations Unit, Medicines and Healthcare Products Regulatory Authority, London, United Kingdom

**KEY WORDS**
pediatric clinical trials, developing countries, drugs, vaccines, biologicals, globalization

**ABBREVIATIONS**
BPCA—Best Pharmaceuticals for Children Act
EEA—European Economic Area
EU—European Union
FDA—Food and Drug Administration
JIA—juvenile idiopathic arthritis
PREA—Pediatric Research Equity Act

The views presented in this article do not necessarily reflect those of the Food and Drug Administration.

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3687
doi:10.1542/peds.2011-3687
Accepted for publication Jul 24, 2012

Address correspondence to Julia Dunne, MD, Medicines and Healthcare Products Regulatory Authority, Special Populations Unit, 151 Buckingham Palace Road, London, UK SW1W 9SZ. E-mail: julia.dunne@mhra.gsi.gov.uk

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2012 by the American Academy of Pediatrics

**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**WHAT’S KNOWN ON THIS SUBJECT:** There is concern about the potential exploitation of children who are enrolled into clinical trials in developing and transition countries. Previous studies of globalization have only examined pediatric drug trials, and only 1 study has provided patient-level data by country.

**WHAT THIS STUDY ADDS:** The involvement of developing and transition countries depends on the product or indication under investigation and is greater for vaccines than for drugs or biologicals. Compared with our previous analysis, involvement of these countries in pediatric drug development has decreased.

**abstract**

**OBJECTIVE:** To examine the characteristics of pediatric trials conducted under US legislation and to compare results with data from 2002 to 2007.

**METHODS:** We reviewed all pediatric trials provided to the US Food and Drug Administration in submissions that were approved between September 28, 2007 and December 21, 2010. We extracted data for each trial including age range, therapeutic indication, design, duration, and patient and center enrollment by location.

**RESULTS:** Overall 346 studies on 113 drugs and biologicals enrolled 55,819 pediatric patients. The United States participated in 86% of the studies, providing 71% of the centers and 74% of the patients. Corresponding percentages for non-US countries were 43%, 29%, and 26% respectively. Developing or transition countries participated in 22% of the studies, providing 12% of the centers and 10% of the patients; our earlier analysis found corresponding percentages of 38%, 12%, and 23%. The most common therapeutic areas studied in the latter countries were infectious, neurologic, and pulmonary diseases. Seventy-eight vaccine studies enrolled 147,692 patients. The United States participated in 40% of the studies, providing 39% of the centers and 22% of the patients. Corresponding percentages for non-US countries were 74%, 61%, and 78% respectively. Developing or transition countries participated in 27% of the studies, providing 15% of the centers and 52% of the patients.

**CONCLUSIONS:** The United States remains an important location for pediatric trials. Developing country involvement in pediatric drug development is not increasing, although these countries participate significantly in vaccine trials. Pediatrics 2012;130:e1583–e1591
For >2 decades, progressive changes in US and, recently, European legislation have created a transatlantic framework of complementary incentives and obligations that are intended to increase the development and availability of age-appropriate medicines for pediatric use.1–6 Consequently, the numbers of pediatric clinical trials are increasing. However, a relatively limited pediatric population is available for enrollment, and the target population may be dispersed geographically. These factors, along with the trends in increasing globalization of clinical research, cause concern about the potential for exploitation in developing and transition countries of the already vulnerable pediatric population.7,8 In 2010, we published an analysis of pediatric drug studies received and assessed by the US Food and Drug Administration (FDA) between February 2002 and March 2007 in response to written requests issued by the FDA under the Best Pharmaceuticals for Children Act of 2002 (BPCA; the “pediatric exclusivity” provision). This is referred to hereafter as the 2002–2007 cohort.9 This was the first published analysis of pediatric clinical trials that provided data on patient enrollment by country. Although most of the studies included ≥1 US center and most of the patients were enrolled in the United States, 38% of the studies included centers in developing or transition countries, and 23% of the patients were enrolled from developing or transition countries. We wished to explore any change in the pattern of study location and patient enrollment for pediatric drug trials, particularly after the entry into force of the European pediatric medicines legislation in January 2007, which introduced a framework that requires earlier development of pediatric clinical trials and supports European pediatric clinical trial networks.5,6 The European legislation may result in increased patient enrollment from the European Union (EU) because, increasingly, sponsors establish global pediatric clinical development programs and subsequently submit the results to both the US and the EU regulatory authorities. We also wished to analyze the locations and patient enrollment for pediatric vaccine trials because we have not done this before.

METHODS
Selection of Studies
We identified all new drugs and biologicals license applications that were approved between September 28, 2007 and December 21, 2010 and submitted to the FDA under either BPCA or the Pediatric Research Equity Act (PREA) of 2003. Within each application, we identified all completed studies that enrolled subjects aged ≤18 years.

Data Collection
For each application submitted to the FDA, individual completed studies that recruited pediatric subjects were identified by the sponsor-allocated trial number. The following data were extracted from each final study report: study location(s), number of trial centers that enrolled pediatric subjects per location, number of pediatric subjects enrolled per location, age range recruited, classification of product (drug, biological, or vaccine), therapeutic indication, study design and duration, study sponsor, and legal basis for submission. Regional categories and the economic status of the participating countries were defined according to the United Nations classification.10

Analysis
To avoid double counting, long-term extensions or substudies of previously counted studies were omitted from the analysis, as were all studies that had been submitted previously to the FDA. The baseline characteristics were summarized by using descriptive statistical analysis. We also present the characteristics of the locations and patient enrollment of the pediatric trials in the 2002–2007 and 2007–2010 cohorts as numbers with percentages. To test whether certain proportions were significantly different between the 2 cohorts, we used a 2-tailed, unpooled Z test. We considered a P value of <.01 to be statistically significant. We used Stata 9 statistical software (State Corp, College Station, TX) for all analyses.

RESULTS
Overview
Overall 139 applications relating to 113 medicinal products (92 drugs, 12 vaccines, and 9 other biological products) met the selection criteria. Nonvaccine biological products are referred to as biologicals. Vaccines are described separately. Twenty-nine applications contained no new pediatric studies. The remaining 110 applications contained 424 new pediatric studies, which enrolled 203 515 pediatric patients. Study characteristics are presented in Table 1. The great majority of the studies were conducted between 2002 and 2009. Most of the studies (66% [280/424]) involved only 1 country, although 71 countries participated altogether.

Sponsors
There were 60 different sponsors; 65% were in the pharmaceutical industry top 5011 and 52% were US-owned. Thirty sponsors conducted trials with centers in ≥1 developing country. Of these sponsors, 73% (22/30) were among the top 50 pharmaceutical companies. Three pharmaceutical companies, GlaxoSmithKline, Merck, and Novartis, conducted 50% (48/96) of the studies involving developing countries; over one-third (38%, 18/48) of these were vaccine studies.

Formulations
Half of the applications (70/139) were for oral formulations (tablets, capsules,
TABLE 1 Characteristics of Studies Submitted in Applications Approved by the FDA Between September 2007 and December 2010 (Cohort 2007–2010)

<table>
<thead>
<tr>
<th></th>
<th>All Products</th>
<th>Drugs</th>
<th>Biologicals</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies (% all studies)</td>
<td>424 (100)</td>
<td>328 (78)</td>
<td>17 (3)</td>
<td>78 (19)</td>
</tr>
<tr>
<td>No. of patients (% all patients)</td>
<td>203 515 (100)</td>
<td>53 662 (26)</td>
<td>2157 (1)</td>
<td>147 692 (73)</td>
</tr>
<tr>
<td>No. of centers (% all centers)</td>
<td>10 483 (100)</td>
<td>8038 (77)</td>
<td>501 (5)</td>
<td>1954 (18)</td>
</tr>
</tbody>
</table>

Study phase

- No. of phase I or I/II studies (% of all studies): 63 (15)
- No. of phase II studies (% of all studies): 79 (18)
- No. of phase II/III or III studies (% of all studies): 270 (64)
- No. of phase IV studies (% of all studies): 12 (3)

Study duration

- <3 mo (% of all studies): 213 (51)
- >3 mo to <6 mo (% of all studies): 65 (15)
- ≥6 mo (% of all studies): 146 (34)

Therapeutic Indications and Therapeutic Area Studied

The studies covered a wide range of indications (n = 60) and therapeutic areas (n = 14). The 3 most commonly studied therapeutic areas overall were infectious diseases, pulmonary/allergy, and psychiatry, together representing 64% of all studies (Fig 1). Vaccine trials accounted for 72% of all enrolled patients. The most frequently studied indications in terms of study number and patient enrollment are listed in Supplemental Tables 7 through 9.

Study Location

Tables 2 through 4 present the top 10 countries involved in the trials, ranked by trial participation and by patient numbers. Table 5 presents data from the earlier cohort of drug studies for comparison. Supplemental Tables 10 through 12 present the participation of all countries by study involvement and patient enrollment. Regional participation is presented in Fig 2. Drugs, biologicals, and vaccines are shown separately. Overall, the United States participated in more trials and enrolled more patients than any other country, and North America participated in more trials than any other region. Just over half (51%) of all studies were conducted entirely outside the United States. The level of involvement of non-US countries increased with increasing trial size, from 36% of trials enrolling <100 patients, to 55% of trials in those enrolling ≥100 patients and 61% of trials in those enrolling >500 patients.

The countries of the EU and European Economic Area (EEA) and Latin America were well represented. The participation of other individual countries and geographical regions varied according to whether the trials involved drugs and biologicals or vaccines.

Role of Developing and Transition Countries and Developing Regions

At a country level, over one-fifth of all trials (23% [96/424]) enrolled patients from ≥1 developing or transition country. Altogether, 41 developing or transition countries contributed to ≥1 pediatric trial. Of the developing or transition countries, Brazil was involved in the most trials, participating in 7% (31/424) of all trials, and Mexico enrolled the most patients, enrolling 7% (14 544/203 515) of all patients. Most of the patients enrolled in Mexico (97%) participated in vaccine trials. Developing countries were relatively more involved in vaccine trials than trials on drugs and biologicals. They supplied 15% (296/1954) of the centers and enrolled 52% (76 772/147 692) of the patients in the vaccine trials and supplied 12% (1027/8539) of the centers and enrolled 11% (6065/55 819) of the patients in the trials on drugs and biologicals. Of the developing regions, Latin America was the most involved in pediatric vaccine trials, participating in as many studies as all of the other developing regions together and enrolling 5 times more patients.

Most of the trials (77% [84/96]) involving developing countries also had centers (and protocol approval) in developed countries. Only 10% (8/78) of vaccine trials enrolling 6% of patients, and

granules, sprinkles, suspensions, or solutions), 28% (39/139) were for topical formulations (administered through skin, lungs, nasal mucosa, or conjunctivae), and the remaining 22% (30/139) were for systemic formulations (injections or infusions).

Age Groups

Adolescents, children, and infants were well represented, but few studies (3.5% [15/424]) included preterm infants or neonates. See Supplemental Fig 3 for a breakdown by age group.

Study Design and Phase

Most of the studies (72% [306/424]) followed a randomized, controlled design. Over one-third (38% [163/424]) were placebo-controlled. Study phase and duration are summarized in Table 1. Most of the trials involving drugs and biologicals (62% [214/346]) focused on efficacy. Pharmacokinetic, safety, and pharmacodynamic studies accounted for 24%, 12%, and 2% of drugs and biologicals trials, respectively. The percentages were similar for trials involving ≥1 developing country. The mean number of patients per trial was 55 for pharmacokinetic studies, 114 for pharmacodynamic studies, 208 for efficacy studies, and 104 for safety studies. The vaccine trials focused on safety and immunogenicity (as a surrogate for efficacy) and enrolled a mean number of 1893 subjects per trial.
1% (4/346) of trials on drugs and biologicals, representing 0.5% of patients, were conducted solely in developing countries. These studies were conducted on the following indications: immunization against diseases caused by Hemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitides, and rotavirus; and the treatment of HIV infection, herpes simplex virus infection, asthma, and acne. The acne study was conducted in 70 adolescents in China.

The most common therapeutic areas studied in the drugs and biologicals trials that included developing countries were pulmonary (asthma) (23%), neurology (migraine, bladder instability, and seizures) (22%), and infectious diseases (fungal and viral diseases) (21%). The least studied therapeutic areas in trials involving developing countries were rheumatology, oncology, and anesthesia.

For a few therapeutic indications, a relatively high percentage of patients were enrolled from developing countries, for

---

**FIGURE 1**
Therapeutic areas represented. A, Drugs, biologicals and vaccines: number of studies by therapeutic area. B, Drugs and biologicals only: patient enrollment by therapeutic area. Vaccines removed to better display the therapeutic areas (Cohort 2007–2010).
example, juvenile idiopathic arthritis (JIA) (26%), bipolar disorder/schizophrenia (29%), and hypertension (34%). However, for the last 2 indications, patients were recruited from 12 and 13 different developing countries, respectively, so patient enrollment in any particular developing country was low (the mean number of patients recruited per developing country was 37 for bipolar disorder/schizophrenia and 44 for hypertension, respectively). A study in JIA recruited 94 patients from Latin America. The same study recruited 27 patients from the United States and 69 patients from Europe.


Tables 4 through 6 compare the involvement of countries and regions in the 2 cohorts of drug studies. Tables 4 through 5 include the top 10 countries involved in drug studies. Latin American representation in the top 10 fell from 5 countries to 1 between the cohorts and was replaced by EU countries and

![Table 2](image)

**TABLE 2** Top 10 Countries Ranked by Study Participation and Patient Enrollment for Studies on Drugs and Biologicals (Cohort 2007–2010)

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Trials (% All Drug and Biologicals Trials) (Total n = 348)</th>
<th>Country</th>
<th>No. of Patients Enrolled (% All Patients in Drug and Biologicals Trials) (Total n = 55 819)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 USA</td>
<td>296 (88)</td>
<td>1 USA</td>
<td>41 375 (74)</td>
</tr>
<tr>
<td>2 Canada</td>
<td>41 (12)</td>
<td>2 Germany</td>
<td>1129 (2)</td>
</tr>
<tr>
<td>2 Germany</td>
<td>41 (12)</td>
<td>3 Poland</td>
<td>1092 (2)</td>
</tr>
<tr>
<td>4 France</td>
<td>32 (9)</td>
<td>4 South Africa</td>
<td>1046 (2)</td>
</tr>
<tr>
<td>4 South Africa</td>
<td>32 (9)</td>
<td>5 Argentina</td>
<td>1044 (2)</td>
</tr>
<tr>
<td>6 Poland</td>
<td>29 (8)</td>
<td>6 Canada</td>
<td>963 (2)</td>
</tr>
<tr>
<td>7 Spain</td>
<td>28 (8)</td>
<td>7 Russia</td>
<td>875 (2)</td>
</tr>
<tr>
<td>8 Argentina</td>
<td>26 (8)</td>
<td>8 France</td>
<td>567 (1)</td>
</tr>
<tr>
<td>9 Russia</td>
<td>24 (7)</td>
<td>9 India</td>
<td>545 (1)</td>
</tr>
<tr>
<td>10 Belgium</td>
<td>23 (7)</td>
<td>10 Australia</td>
<td>468 (1)</td>
</tr>
<tr>
<td>10 Italy</td>
<td>23 (7)</td>
<td>11 Brazil</td>
<td>483 (1)</td>
</tr>
</tbody>
</table>

**FIGURE 2**

Regional participation in studies and patient enrollment for drugs, biologicals, and vaccines.
Russia for study involvement and by EU countries, Russia, and Australia for patient enrollment. Table 6 includes a statistical comparison of the 2 cohorts. There was a statistically significant decrease in both the number of drug studies involving ≥1 developing or transition country and the number of patients enrolled in these countries. Statistically significant decreases were also seen for drug studies conducted in Latin America and non-US countries. In contrast, there was a statistically significant increase in patient enrollment (but not study involvement) for the United States and for EU and EEA countries. There was no significant change in the percentage of studies conducted entirely outside the United States. However, there was a statistically significant increase in the proportion of US-only studies. For drug studies only, the most frequently studied therapeutic areas were, in descending order, pulmonary/allergy, infectious diseases, and psychiatry, representing 59% of drug studies. This compares with infectious diseases, psychiatry, and metabolism/endocrinology, representing 57% of drug studies, in the 2002–2007 cohort. The most common therapeutic areas studied in drug trials that included centers in developing countries also differed between the cohorts. Infectious disease was the most common area studied in both periods. Neurology and pulmonary/allergy were the next most frequently studied areas for the 2007–2010 cohort, whereas cardiology, metabolism and endocrinology, and neurology were the next most frequently studied areas for the 2002–2007 cohort.

**PREA Versus BPCA**

The majority of studies (87%) in the 2007–2010 cohort were conducted under PREA. Fewer studies conducted under PREA involved developing countries than did studies conducted under the exclusivity provision (BPCA) (20% vs 40%). The indications studied under BPCA and PREA were also different. For example, all the psychiatry studies conducted under PREA involved attention-deficit/hyperactivity disorder or autism, and none included developing countries. In contrast, all the psychiatry studies conducted under BPCA involved schizophrenia, and 23% included developing or transition countries (Puerto Rico and Russia). There was no difference in trial size between drug trials conducted under PREA and those conducted under BPCA. We cannot explain the differences, although it may reflect the use of BPCA to encourage the study of rarer pediatric indications for which international trials may be necessary to recruit sufficient patient numbers.

**DISCUSSION**

The data presented do not support concerns that pediatric subjects in developing countries are being exploited to develop pediatric medicines for developed countries. Countries such as India and China are often cited as emerging locations for clinical trials because of the large number of potential research participants and the lower cost of research in these countries.12–14 Our data do not support this claim with respect to pediatric drug trials, because we have found only a minimal increase in activity in these 2 countries between the 2 cohorts. In addition, the number of developing countries represented in the top 10 countries involved in pediatric drug trials by study involvement and patient enrollment has fallen.

These data indicate a similar decreased involvement of developing regions. Compared with the 2002–2007 cohort, the 2007–2010 cohort contains fewer studies that include ≥1 center in a developing country, and there is lower

---

**TABLE 3** Top 10 Countries Ranked by Study Participation and Patient Enrollment for Studies on Vaccines (Cohort 2007–2010)

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of trials (% All Vaccine Trials)</th>
<th>Country</th>
<th>No. of Patients Enrolled (% All Vaccine Trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Total n = 78)</td>
<td></td>
<td>(Total n = 147,692)</td>
</tr>
<tr>
<td>USA</td>
<td>32 (40)</td>
<td>USA</td>
<td>32,578 (22)</td>
</tr>
<tr>
<td>Germany</td>
<td>14 (17)</td>
<td>Mexico</td>
<td>13,857 (9)</td>
</tr>
<tr>
<td>Canada</td>
<td>12 (15)</td>
<td>Finland</td>
<td>12,665 (9)</td>
</tr>
<tr>
<td>Finland</td>
<td>11 (14)</td>
<td>Peru</td>
<td>12,547 (8)</td>
</tr>
<tr>
<td>Brazil</td>
<td>10 (12)</td>
<td>Germany</td>
<td>11,213 (8)</td>
</tr>
<tr>
<td>Colombia</td>
<td>8 (10)</td>
<td>Argentina</td>
<td>7,790 (5)</td>
</tr>
<tr>
<td>UK</td>
<td>8 (10)</td>
<td>Colombia</td>
<td>6,140 (4)</td>
</tr>
<tr>
<td>Spain</td>
<td>7 (9)</td>
<td>Venezuela</td>
<td>5,222 (4)</td>
</tr>
<tr>
<td>Australia</td>
<td>6 (7)</td>
<td>Brazil</td>
<td>5,049 (3)</td>
</tr>
<tr>
<td>Poland</td>
<td>6 (7)</td>
<td>Honduras</td>
<td>4,463 (3)</td>
</tr>
</tbody>
</table>

---

**TABLE 4** Top 10 Countries Ranked by Study Participation and Patient Enrollment for Studies on Drugs (Cohort 2007–2010)

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of trials (% All Drugs Trials)</th>
<th>Country</th>
<th>No. of Patients Enrolled (% All Drugs Trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Total n = 329)</td>
<td></td>
<td>(Total n = 53,662)</td>
</tr>
<tr>
<td>USA</td>
<td>281 (85)</td>
<td>USA</td>
<td>40,192 (75)</td>
</tr>
<tr>
<td>Canada</td>
<td>40 (12)</td>
<td>South Africa</td>
<td>10,025 (2)</td>
</tr>
<tr>
<td>Germany</td>
<td>36 (11)</td>
<td>Poland</td>
<td>10,025 (2)</td>
</tr>
<tr>
<td>South Africa</td>
<td>30 (9)</td>
<td>Canada</td>
<td>9,40 (2)</td>
</tr>
<tr>
<td>France</td>
<td>29 (9)</td>
<td>Argentina</td>
<td>8,88 (2)</td>
</tr>
<tr>
<td>Poland</td>
<td>28 (9)</td>
<td>Russia</td>
<td>8,75 (2)</td>
</tr>
<tr>
<td>Spain</td>
<td>25 (8)</td>
<td>Germany</td>
<td>7,78 (1)</td>
</tr>
<tr>
<td>Argentina</td>
<td>24 (7)</td>
<td>India</td>
<td>5,45 (1)</td>
</tr>
<tr>
<td>Russia</td>
<td>24 (7)</td>
<td>France</td>
<td>5,21 (1)</td>
</tr>
<tr>
<td>Belgium</td>
<td>22 (7)</td>
<td>Australia</td>
<td>4,78 (1)</td>
</tr>
</tbody>
</table>
TABLE 5 Top 10 Countries Ranked by Study Participation and Patient Enrollment for Studies on Drugs (Cohort 2002–2007)

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of Trials (%) All Drug Trials (Total n = 201)</th>
<th>Country</th>
<th>No. of Patients Enrolled (%) All Patients in Drug Trials (Total n = 19,563)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 USA</td>
<td>178 (89)</td>
<td>1 USA</td>
<td>13,142 (67)</td>
</tr>
<tr>
<td>2 Canada</td>
<td>43 (21)</td>
<td>2 Costa Rica</td>
<td>1,380 (7)</td>
</tr>
<tr>
<td>3 Mexico</td>
<td>33 (18)</td>
<td>3 Argentina</td>
<td>632 (3)</td>
</tr>
<tr>
<td>4 Brazil</td>
<td>28 (14)</td>
<td>4 Mexico</td>
<td>510 (3)</td>
</tr>
<tr>
<td>5 Germany</td>
<td>27 (13)</td>
<td>5 Netherlands</td>
<td>404 (2)</td>
</tr>
<tr>
<td>6 Argentina</td>
<td>20 (10)</td>
<td>6 Germany</td>
<td>403 (2)</td>
</tr>
<tr>
<td>7 Chile</td>
<td>19 (9)</td>
<td>7 Brazil</td>
<td>400 (2)</td>
</tr>
<tr>
<td>8 Peru</td>
<td>19 (9)</td>
<td>8 Chile</td>
<td>358 (2)</td>
</tr>
<tr>
<td>9 Netherlands</td>
<td>18 (9)</td>
<td>9 Gabon</td>
<td>330 (2)</td>
</tr>
<tr>
<td>10 South Africa</td>
<td>17 (8)</td>
<td>10 India</td>
<td>224 (1)</td>
</tr>
</tbody>
</table>

* Data set of studies with complete data on location (n = 201 studies).

Patient enrollment from developing countries. The shift reflects increased patient recruitment in the United States and decreased recruitment in Latin America, the lead developing region involved in pediatric trials. The decrease in Latin American participation may be due partly to the small number of antibiotic trials in the current sample. In the earlier cohort, the region was principally involved in large trials on antibiotics. There was no significant change in EU participation in clinical trials with respect to study involvement, although there was a statistically significant, albeit small, increase in patient enrollment. This is not surprising, because the EU pediatric legislation did not enter into force until 2007.

As noted previously, there was a difference between the 2 cohorts in the therapeutic areas studied most commonly in developing countries, from infectious diseases, cardiology, metabolism and endocrinology, and neurology, to infectious diseases, neurology, and pulmonary/allergy. Arguably this change is reassuring, because asthma is becoming a major health issue in many developing countries. The neurologic indications studied in developing countries in the 2007–2010 cohort were seizures, neurogenic bladder, and migraine. Pediatric seizures are a serious condition, and the prevalence is higher in developing countries than in the United States. Neurogenic bladder is also a common pediatric problem in developing countries, and the serious potential morbidity justifies involvement of these countries in the relevant clinical trials. Pediatric migraine was studied in Latin America, where the prevalence of migraine is similar to that in the United States and Europe.

It was noted that for a few therapeutic areas, such as JIA, bipolar disorder/schizophrenia, and hypertension, a relatively high percentage of patients were recruited from developing or transition countries. Although they do not present a major public health problem, these conditions occur in developing countries, and the participating countries enrolled relatively small numbers of patients. Taking into account the epidemiology of the condition under study, the number of patients enrolled from a country, and the size of its pediatric population, few patients (<0.2%) from developing countries were included in studies that could be described as irrelevant or inappropriate for that particular country.

This study is limited because we have no earlier data for vaccine trials, and so it is not possible to comment on any regional changes over time in trial location or patient involvement. However, we now have baseline data with which to compare vaccine trial locations in a future cohort. Another limitation is the method used to obtain the cohort of studies. Our method captures 100% of the submitted pediatric studies that were evaluated under the FDA pediatric legislative provisions between September 2007 and December 2010. Because the FDA does not archive study data according to the dates of study enrollment, its databases cannot be searched for studies that enrolled patients during a particular time period. There is probably some overlap between the last enrollment period of the drug studies in the earlier cohort compared with the earliest enrollment period of drug studies in the later cohort. Finally, we used a UN classification of countries and regions that is based on economic indices only. There is another UN classification which combines social and economic indicators into a composite Human Development Index, which serves as a frame of reference for both social and economic development. Although not without its critics, the Human Development Index may be a more appropriate classification of developing countries. However, we used the economic classification, because it has been used by other investigators who have published recently on this topic.

CONCLUSIONS

The data presented do not support concerns that the globalization of clinical trials is leading to an inappropriate or increasing involvement of developing countries in pediatric clinical trials. In the earlier cohort, 62% of drug studies involved non-US sites and 38% involved developing or transition countries, whereas in the 2007–2010 cohort, only 43% of drug studies involved non-US sites and 22% involved developing or transition countries. Overall, we found that less than half of all pediatric studies (49%) submitted to the FDA...
contained sites outside the United States and approximately one-fifth (23%) involved developing or transition countries. For drugs and biological trials, the great majority of patients (89%) were recruited from developed countries, whereas, for vaccine trials, a lesser majority of patients (52%) were enrolled from developing countries.

In general, the most commonly studied therapeutic areas in developing or transition countries were appropriate for their public health needs and patients were not enrolled into studies inappropriately from this perspective. Regulatory authorities and other stakeholders should continue to review the locations of pediatric clinical trials, the numbers of patients enrolled per location, and the design of the trials and the indications studied. Our current analysis provides a useful set of benchmarks against which to measure future changes in the involvement of developing or transition countries in pediatric clinical trials.

ACKNOWLEDGMENTS

The authors thank Renan Bonnel and Debbie Avant for their support in data extraction from the FDA electronic document room and data store, and Gerold Wharton for the statistical analysis.

REFERENCES


The Globalization of Pediatric Clinical Trials
Julia Dunne, M. Dianne Murphy and William J. Rodriguez
Pediatrics 2012;130;e1583; originally published online November 5, 2012;
DOI: 10.1542/peds.2011-3687

Updated Information & Services
including high resolution figures, can be found at:
/content/130/6/e1583.full.html

Supplementary Material
Supplementary material can be found at:
/content/suppl/2012/10/30/peds.2011-3687.DCSupplemental.html

References
This article cites 8 articles, 1 of which can be accessed free at:
/content/130/6/e1583.full.html#ref-list-1

Citations
This article has been cited by 7 HighWire-hosted articles:
/content/130/6/e1583.full.html#refated-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Medical Education
/cgi/collection/medical_education_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2012 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.
The Globalization of Pediatric Clinical Trials
Julia Dunne, M. Dianne Murphy and William J. Rodriguez

*Pediatrics* 2012;130;e1583; originally published online November 5, 2012;
DOI: 10.1542/peds.2011-3687

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/130/6/e1583.full.html