GLOBALIZATION FACILITATES PEDIATRIC DRUG TREATMENT IN THE 21ST CENTURY

Introduction

US legislation, supported by strengthened ethical frameworks and improved trial design, has produced significant increases in the number of pediatric clinical trials. This has global implications.

Method

We reviewed all submissions of pediatric data received by the US FDA from 2002-2007 in response to new FDA pediatric initiatives.

Results

Although 54% of the trials were multinational, the US dominated as a trial location. The European Union (EU) and Latin America followed. Few trials specifically studied neonates, infants and toddlers.

Although most pediatric drug programmes are global, the US remains the dominant location for pediatric trials. This distribution differs for adult trials. The balance may change in the future. EU and FDA regulators should continue to discuss coordinated approaches to minimize unnecessary pediatric trials and to optimize trial design, safety and conduct so that the limited pediatric populations available are enrolled only in ethically implemented, scientifically important trials.

Conclusion

INTRODUCTION

A historical reluctance to study medicines in children has necessitated decades of off-label use for most pediatric prescribing.[1,2,3] Ethical concerns and the difficulties of conducting trials in children fueled the reluctance, which was exacerbated by the lack of sufficient commercial returns for the pharmaceutical industry.[4] This unacceptable situation, however, is changing. More robust ethical, regulatory and legal frameworks exist to ensure the protection of children, who can neither volunteer nor give informed consent to take part in trials.[5,6,7] Furthermore, it is agreed that children are not small adults[8] and pediatric trials are needed to establish the correct dose, efficacy and safety of a medicine in that population.[9,10] Increasing involvement of pediatric expertise has improved the design and conduct of these trials. Finally, important changes in US legislation both provided financial incentives and imposed requirements on the pharmaceutical industry to study medicines in children.[11,12] This has produced a significant increase in the number of pediatric trials conducted since 1997.[10] The European Union pediatric medicines regulations, which were adopted in 2007, are also based on a framework of incentives and requirements and will lead to a further stimulation of pediatric drug development.[13] We wished to explore the location and other characteristics of recently conducted pediatric trials in view of the relatively small and geographically scattered pediatric

population which is available to participate in trials and in view of the increasing globalization of drug development. In particular we wished to explore whether, as with adult clinical trials, sponsors are shifting the location of pediatric trials away from the United States. [14,15] We undertook a descriptive study of dossiers submitted by the pharmaceutical industry in response to FDA's issuance of written requests for pediatric data on products that were already authorised for use in adults. If performed as requested, responses to FDA written requests can provide additional market exclusivity for the sponsor. We analyzed the information from a 5 year period according to trial location and, where available, patient numbers. We also examined the age ranges studied, location specific and sponsor specific characteristics, and differences between national and multinational trials.

METHODS

The data set comprised 99 submissions received by FDA from February 2002 to March 2007 in response to FDA written requests issued under the Best Pharmaceuticals for Children Act of 2002 (BPCA). The start date in 2002 was chosen because many submissions were electronic from that point. The cut-off date was determined by the start of the study. We limited our analysis to trials submitted pursuant to BPCA 2002 because this legislation required the tracking of specific data for these pediatric submissions including the number of trial centers and geographic location when available.

We extracted data that related to country, center and patient participation in pediatric trials, products and indications studied and the trial sponsors. It was not feasible analyze trends in trial size, design or location over the five year period because many of the trials took place over long time periods and information on trial start date was not always readily available. Sources of information supplementing the analysis were internal descriptors on drugs granted pediatric exclusivity, summary of exclusivity determinations, the FDA electronic document room (EDR), and the FDA division file system (DFS). The data were collected by L.M. and D.A and analyzed descriptively by J.D. and L.M. This study has several limitations which result from restricting the analysis to data submitted pursuant to BPCA. BPCA provided an incentive program in which sponsors receive a financial incentive (pediatric exclusivity) in response to submitting pediatric data that comply with an FDA Written Request for pediatric studies. Thus the studies in this dataset are all sponsored by the pharmaceutical industry. The pharmaceutical industry influences the products and indications studied under BPCA, as most Written Requests issued by the FDA respond to an initial proposal by a sponsor to conduct pediatric studies. As the incentive to the sponsor is pediatric exclusivity, there is a commercial driver for the sponsors' proposals to focus on drugs for which additional market exclusivity will provide a greater financial return to the sponsor rather than on drugs that will provide greater therapeutic benefit to the pediatric population. Also, older off-patent products cannot take advantage of the incentive programme as the incentives do not apply if the period of patent protection or market exclusivity has expired for the drug.[16] Finally,

vaccines and biological products are outside the scope of BPCA, and so are not represented in this study.

RESULTS

OVERVIEW

The 99 submitted applications included 257 pediatric trials (average 2.6 trials per application; range 1 – 9). The applications were submitted by 48 pharmaceutical companies and covered approximately 60 indications. Most of the companies (87%) were in the top 50 pharmaceutical companies in the world based on 2007 global sales.[17] Seventy percent of the companies were based in the US; the remainder were based in Western Europe.

The trials were distributed across more than 60 countries and included at least 5850 centers and 46,000 subjects. The median and mean numbers of countries taking part per trial, were 2 and 3.5 respectively (range 1-18).

Data on country and center involvement were available for approximately 80% of all trials submitted (201/257). Data on center involvement were restricted to the number of centers per country; the center location within the country was not recorded. Of these 201 trials, patient numbers per country were available for 119 trials (60% of all trials submitted).

All of the products were already authorised for use in adults. The majority of the products tested were in tablet or capsule form (68%). The remainder were intravenous (14%), topical (11%), or inhaled formulations (3.5%). There was also a small number of products (3.5%) for which both the tablet and intravenous formulations were tested.

TABLE I

Ranking of Top 10 Countries by Study, Center, or Patient Number									
	Country	No studies* (% total n=201)		Country	No centers* (% total n=5471)		Country	No patients** (% total n=19506)	Ave no patients
1	USA	178 (89)	1	USA	3,984 (73)	1	USA	13,142 (67)	122
2	Canada	43 (21)	2	Canada	154 (3)	2	Costa Rica	1,360 (7)	194
3	Mexico	33 (16)	3	Russia	116 (2)	3	Argentina	632 (3)	70
4	Brazil	28 (14)	4	Germany	106 (2)	4	Mexico	510 (3)	57
5	Germany	27 (13)	5	Mexico	100 (2)	5	Netherlands	404 (2)	58
6	Argentina	20 (10)	6	Brazil	89 (2)	6	Germany	403 (2)	50
7	Chile	19 (9)	7	Argentina	76 (1)	7	Brazil	400 (2)	33
8	Peru	19 (9)	8	India	60 (1)	8	Chile	358 (2)	36
9	Netherlands	18 (9)	9	Poland	52 (1)	9	Gabon	330 (2)	330
10	South Africa	17 (8)	10	France	50 (1)	10	India	224 (1)	45

**** dataset of studies with complete data on location and center number (n=201 studies)***
***** dataset of studies, with complete data on location, center number, and patient number (n=119 studies).***
The ranking by patient numbers is skewed by seven studies on levofloxacin which were conducted in Latin America, and led to the inclusion of Costa Rica in the top ten.

TRIAL LOCATION

Table I shows the ranking of the top ten countries involved in the pediatric clinical trials as sorted by trial involvement, center numbers or patient numbers.

The US was the greatest contributor by far. It was involved in 89% of the trials, was the location for 73% of the centers and contributed 67% of the patients. This represented four times more trials and twenty-six times more centers than second-place Canada and ten times more patients than second-place Costa Rica. Four other countries (Mexico, Brazil, Germany and Argentina) also appeared in all three top ten rankings.

Figure 1 shows the other top three regions by number of centers: Latin America (8%), Western Europe (8%) and Eastern Europe [including Russia] (5%). Again their contribution was relatively small compared with that of the US. Africa and the Asia-Pacific were only represented in a small percentage of the trials and none of the pediatric trials in the submissions were conducted in mainland China or Japan.

TYPES OF TRIALS

The trials ranged from phase I to IV[18] (27% phase I, 2% phase I/II, 14% phase II, 7% phase II/III, 41% phase III, and 9% phase IV) and varied considerably in organizational complexity from a national (US) three center pharmacokinetic study in 24 patients to a double blind placebo controlled safety and efficacy trial in which 177 patients were recruited by 42 centers across 18 countries and 3 continents.

The product for which most patients were studied was levofloxacin, for which 4614 patients were recruited from 9 countries (mainly in Latin America) into 7 trials.[19] This included the largest individual trial for any product, a safety trial in approximately 2,000 patients.

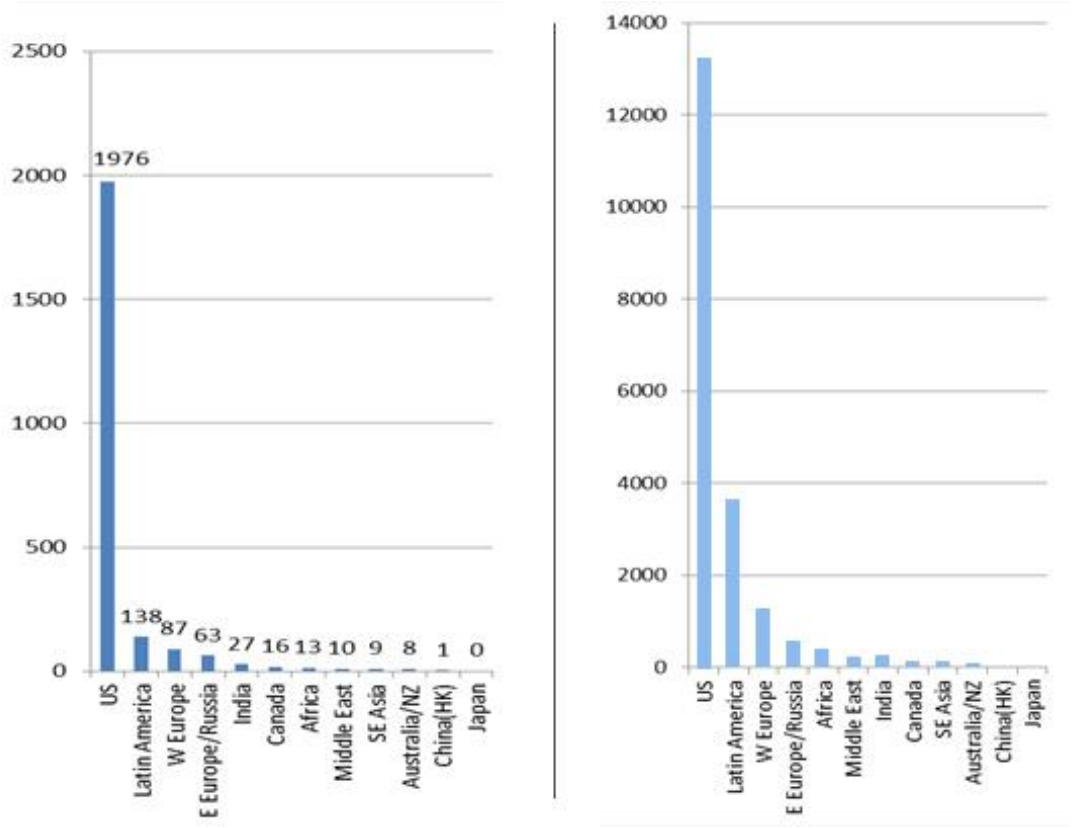
PRODUCTS AND INDICATIONS STUDIED

The most commonly studied indications were bacterial infection (including conjunctivitis, community acquired pneumonia and complicated urinary tract infection), cancer, depression, hypertension, partial seizures, schizophrenia, juvenile idiopathic arthritis, attention deficit hyperactivity disorder (ADHD), human immune deficiency virus (HIV) infection, and detrusor hyperreflexia (Table II).

The United States was involved in trials covering all of the studied indications apart from malaria and type I diabetes.

Apart from a concentration of trial centers for studies on antibiotics in Latin America, there was no clear relationship between country/region and indication studied. All but five trials with centers in developing countries also had centers (and therefore protocol and ethical approval) in the US, Canada, or Western Europe. The country locations for the five exceptions were appropriate choices in terms of the prevalence and seriousness of the condition studied (Gabon: malaria; Brazil, Argentina, South Africa, Romania: HIV infection; South Africa: heterozygous familial hypercholesterolemia.) There was insufficient information available to assess the integrity of the recruitment procedures or informed consent procedures in the developing countries.

FIGURE I



A. Number of centers per country/region	*B. Number of patients per country/region*

These bar graphs show the number of centers and patients per country or, per region in the world involved in pediatric clinical trials. The United States is the greatest contributor (73% of the centers and 67% of the patients) followed by Latin America (8%), Western Europe (8%), and Eastern Europe (including Russia, 5% . Africa and Asia- Pacific region are only represented in a small percentage of the trials and none of the pediatric trails in the submissions were conducted in mainland China or Japan.

AGE GROUPS STUDIED

Overall, 70% of the trials included adolescents ie age 12 -18 years. The age groups most commonly studied were the 0-18 years, 6-18 years and 12-18 years categories; each represented around 20% of the trials (Figure II). Few trials targeted neonates, or infants and toddlers (7.5%). This is not surprising as there are no specific incentives under BPCA to study the younger age groups, especially the neonatal population. The indications studied specifically in neonates were HIV infection, ophthalmia neonatorum and other bacterial infections. Indications studied specifically in infants and toddlers were HIV infection, partial seizures, and allergic rhinitis/asthma. There was no correlation between country and age groups studied.

Only five countries took part in the five neonatal trials: Brazil, Chile, Mexico,

South Africa and the United States. This may reflect the indications under study. About one third of the countries took part in at least one trial on infants and toddlers (from US, Canada, Latin America, European Union and the Middle East). The United States was involved in trials covering all of the age categories.

TABLE II
Indications Studied: *Indication Followed by Number of Studies (No. International)*

Attention Deficit Hyperactivity Disorder [ADHD] **6(0)**	Detrusor hyperreflexia 7(4)	Obesity 4(1)
ADHD-insomnia **1(0)**	Diabetes Mellitus type I **2(1)**	Ophthalmia Neonatorum **2(0)**
Adolescent-Onset Bipolar disorder **4(3)**	Diabetes Mellitus type II **6(4)**	Opioid-tolerant pediatric patients on around-the-clock opioid therapy and having breakthrough pain **1(1)**
Adolescent-Onset Schizophrenia **4(3)**	End Stage Renal Disease **1(0)**	Organ rejection prevention in renal allograft **2(2)**
Asthma **4(2)**	Gastroesophageal Reflux Disorder [GERD] **4(1)**	Osteogenesis imperfecta **2(1)**
Asthma/allergic rhinitis **1(0)**	Glaucoma **6(4)**	Partial seizures **11(8)**
Bacterial Conjunctivitis **1(1)**	Heart failure **3(0)**	Preparative regimen for allogeneic hematopoietic stem cell transplantation **1(0)**
Bacterial infection **10(8)**	Heterozygous familial hypercholesterolemia **7(4)**	Prevent nausea and vomiting in post-op and chemotherapy **3(2)**
Bone mineral density in anorexia nervosa patients **1(0)**	HIV infection **7(4)**	Prevention and treatment of thromboses in patients with heparin induced thrombocytopenia and thrombosis syndrome **1(0)**
Cancer **30(15)**	Hypertension **16(9)**	Refractory ALL or AML and Non-Hodgkin's lymphoma **2(0)**
Community acquired pneumonia **7(4)**	Hypothalamic obesity **1(1)**	Seasonal Allergic Rhinitis **1(1)**
Complicated UTI, Acute pyelonephritis **3(3)**	Influenza A & B **1(1)**	Tinea capitis **5(4)**
Critical Arrhythmias **1(1)**	Iron deficiency due to chronic hemodialysis **1(1)**	***[201 studies]***
Depression **7(3)**	Juvenile Idiopathic Arthritis **8(7)**	
Depression /generalized anxiety disorder **6(0)**	Maintenance treatment of asthma/allergic rhinitis/severe atopic dermatitis **2(1)**	
Depression/obsessive compulsive disorder **6(4)**	Malaria **3(1)**	
	McCune-Albright Syndrome **1(0)**	
	Migraine **6(1)**	
	Molluscum contagiosum **3(0)**	
	Narcolepsy **3(3)**	

DIFFERENCES BETWEEN NATIONAL AND MULTINATIONAL TRIALS

Less than 50% of the trials were conducted in one country only, ie national, and 87% of these national trials were conducted in the United States (40% of all trials for which data were available). The smaller earlier phase trials tended to be national whereas the larger, later phase trials tended to be multinational.

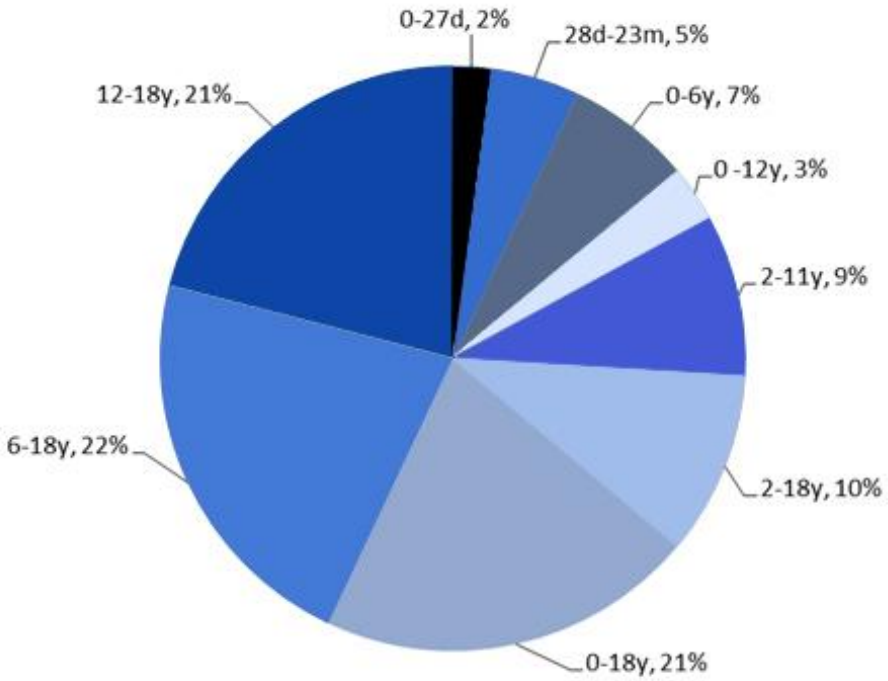
Over 70% of the pediatric data sets submitted contained at least one multinational trial. Some indications, such as ADHD, ADHD-associated insomnia, and generalized anxiety disorder were studied only in national trials based in the US. Multinational trials predominated over national trials in the areas of metabolism and endocrinology, immunology and infectious diseases, oncology, ophthalmology and rheumatology.

A minority of sponsors only conducted national trials. They were mostly small US-based companies.

The results of the trials were reviewed for evidence of possible regional effects. Data from centers in Russia were considered to have driven the positive results for a pivotal trial on the treatment of adolescent schizophrenia with olanzapine. However, FDA inspection of the Russian centers found no evidence of bias.[20] For the antidepressant citalopram, the two pivotal trials yielded divergent results. One, based solely in the US, was positive. One, based in Europe, was negative. There is no suggestion in the review that geographic region affected the results.[21] The results of a trial in partial seizures revealed a discrepancy in the median percentage changes from baseline between the US and non-US centers in the pivotal trial. Further analyses indicated that this was due to differences in drug exposure levels between US and non-US centers, and not to response differences. The higher drug levels in patients from the non-US centers appeared to be related to the higher proportion of subjects in those centers receiving concomitant medication with the enzyme-inhibitor valproic acid.

In retrospect, the usual cause for a failed or uninterpretable trial was failure to identify the correct dose, inadequate trial design/execution or inadequate power. No trial was the subject of an FDA compliance action.

FIGURE II: Percentage of Studies According to Age Entry Criteria



This pie chart shows the age groups most commonly studied in pediatric trials. The most common studies groups were adolescents, ages 12-18 years (about 70%). Few trials targeted neonates or infants and toddlers (7.5). (Total n=201 studies)

DISCUSSION

The majority of pediatric trials conducted under BPCA and submitted to FDA between 2002 and 2007 were multinational. Seventy percent of the products studied in this sample included at least one multinational trial in their dataset; 54% of the individual trials were multinational. The United States was the dominant location for pediatric trials, being involved in 89% of trials (as the sole involved country in 40% of trials) and contributing 73% of centers and 67% of patients. However, the United States may lose this dominance with further globalization of pediatric drug development programmes. There is evidence that this has already happened with adult clinical trials. A recent survey of industry-sponsored phase 3 trials which were reported in three journals from 1995 to 2005 found a shift away from centers in the US and Western Europe. In addition 31% of trials on the ClinTrials.gov registry recruiting patients in 2007 were conducted solely outside the US and 56% of the trial centers were outside the United States.[14] In this study the EU contributed 11% of the centers and 7% of patients in the pediatric trials submitted to FDA. Following adoption of the European Union pediatric regulations in 2007[22], which include new incentives and requirements to conduct pediatric development programmes, there may be more interest in conducting trials in the EU. Implementation of this new legislation is already stimulating an increase in pediatric drug development programmes.[23] A number of EU member states have created national pediatric clinical trial networks in anticipation of

an increased interest in siting pediatric clinical trials in the EU.[24,25,26] There are also existing European pediatric clinical trial networks based on therapeutic areas which provide a framework for multicountry trials. [27,28,29]

Of the developing regions, Latin America contributed 6% of the centers and 18% of patients. This was more than any other geographical region after the United States and is a relatively greater contribution than has been found in studies of the globalization of trials in adults. Other predominantly developing regions however, such as Africa and Asia-Pacific, were involved relatively infrequently in pediatric trials submitted to FDA. Reasons for this are unknown as the trial centers are selected by the sponsor, but may include cultural differences, the nature of the indications under study and the lack of specific pediatric legislation in those regions. The low costs, comparatively light regulatory burden and large, treatment-naïve patient pools of some developing regions may attract sponsors of clinical trials. However, these advantages would need to be weighed against other important factors in determining pediatric clinical trial locations including the ability to recruit adequate numbers of pediatric patients in a timely fashion, the need for centers with appropriate pediatric expertise and clinical trial experience, and the local ethical or cultural climate.

Although a broad range of products were studied in this sample, the most commonly studied indications do not necessarily reflect greatest pediatric therapeutic need; the potential commercial return associated with pediatric exclusivity granted to a particular product is also an important factor.[30]

A striking finding was the relatively small proportion of trials in neonates and infants, despite the pressing need for more information in this population. This was not unexpected as there are few incentives under BPCA to specifically study the younger age groups. The new US and EU legislation mandates trials in all appropriate age groups, including the very young, and so this imbalance should change in the future.

The US and EU legislation, with their requirements and incentives to conduct pediatric trials, strengthen the influence of US and EU regulators over pediatric drug development. But as well as guiding the development of safe, properly tested pediatric medicines, regulators also share a responsibility to protect children from harm. Since September 2007 EU and US regulators have held regular reviews and discussions of scientific and ethical issues concerning pediatric development programs. The aim is to avoid the enrolment of children in unsound, unnecessary or unethical trials and to alert each other to developing safety concerns. Topics for discussion have included the development of products to treat migraine, retinopathy of prematurity and types I and II diabetes, and specific exchanges on, for example, tumour necrosis factors, enrolment of neonates in antiepileptic trials, use of spacer devices in metered dose inhaler trials, the risk/benefit of long acting beta agonists, and the safety of erythropoietin stimulating agents for treatment of anemia associated with chemotherapy. Vaccines and biological products are included as they now fall within the scope of both EU and US pediatric medicines legislation. The discussions are important in developing a common understanding on approach and have

also identified issues which were previously unknown to at least one of the parties including new safety concerns, the existence of ongoing trials and changes in trial conduct. Extension of the arrangement to include active participation of regulators from other regions is under consideration.

CONCLUSION

The globalization of clinical research extends to pediatric drug development programmes, although, in this sample at least, the United States is still the major contributor at all levels of study involvement. Country and regional trends in trial participation may change as the number of pediatric trials increases, stimulated by new regional legislation. This study is a first step in providing regulatory oversight of pediatric drug programmes, in line with FDA's mission as a public health agency.[31]

AUTHORS

Julia Dunne MA, MD
Office of Paediatric Therapeutics, Food and Drug Administration
Silver Spring, Maryland* (*corresponding author – contact details below*)

Lala Margaryants PharmD
Scientific Centre of Drug and Medical Technology Expertise, Yerevan, Republic of Armenia **

M. Dianne Murphy MD
Office of Paediatric Therapeutics, Food and Drug Administration
Silver Spring, Maryland

Ann M. Myers, RPh, MPH
Office of Paediatric Therapeutics, Food and Drug Administration
Silver Spring, Maryland

Debbie Avant RPh
Office of Paediatric Therapeutics, Food and Drug Administration
Silver Spring, Maryland

William J. Rodriguez MD, PhD
Office of Paediatric Therapeutics, Food and Drug Administration
Silver Spring, Maryland

Correspondance Address and Contact Details for Dr. Dunne
Food and Drug Administration
10903 New Hampshire Avenue, Building 32, Room 5154
Silver Spring, MD 20993, USA.
(Email: julia.dunne@fda.hhs.gov) Phone: 301-796-8658 Fax: 301-847-8640

**Julia Dunne is currently seconded to the FDA from the Medicines and Healthcare products Regulatory Agency, London, UK*

***Lala Margaryants was a Hubert Humphrey Fellow on assignment to the FDA from May-September, 2007*

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