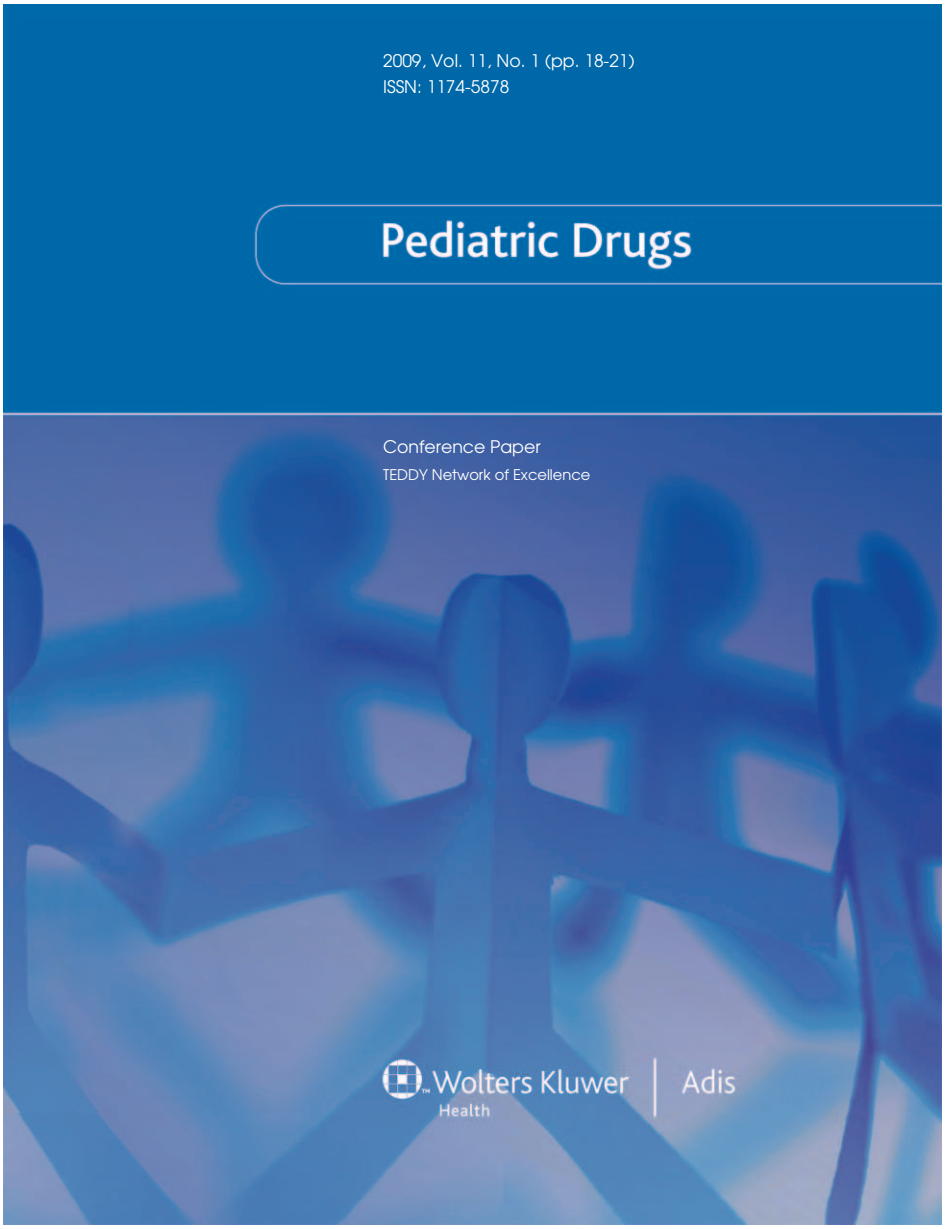

CONFERENCE PAPER

Pediatr Drugs 2009; 11 (1): 18-21
1174-5878/09/0001-0018/$49.95/0

The Task-force in Europe for Drug Development for the Young (TEDDY) Network of Excellence

Adriana Ceci,[1] *Carlo Giaquinto*,[2] *Jean-Pierre Aboulker*,[3] *Paola Baiardi*,[1] *Fedele Bonifazi*,[4] *Oscar Della Pasqua*,[5] *Alfredo Nicolosi*,[6] *Domenica Taruscio*,[7] *Miriam Sturkenboom*[8] and *Ian Wong*[9]

1 Consorzio per Valutazioni Biologiche e Farmacologiche, Pavia, Italy
2 Azienda Ospedaliera di Padova, Padova, Italy
3 Institut National de la Sante et Recherche Medicale (INSERM), Villejuif, France
4 IRIDIA Health Care Engineering, Bari, Italy
5 Leiden/Amsterdam Center for Drug Research, Leiden, the Netherlands
6 Consiglio Nazionale delle Ricerche, Istituto di Tecnologie Biomediche, Milano, Italy
7 Istituto Superiore di Sanità, Roma, Italy
8 Erasmus University Medical Center, Rotterdam, the Netherlands
9 School of Pharmacy, University of London, London, England

Abstract

The Task-force in Europe for Drug Development for the Young (TEDDY) was established in 2005 to contribute to the promotion of safe and efficacious medicines for children in the context of the impending European Paediatric Regulation that finally came into force in January 2007. The project includes seven objectives and 12 Work-Packages encompassing the main aspects of the development and use of pediatric drugs. TEDDY represents a new entity in the pediatric pharmaceutical field, differing from a Scientific Society, a network for developing research or trials, or a consultative regulatory body. The ambition of TEDDY is to support the existing pediatric networks, societies, and regulatory bodies in performing innovative initiatives, including those in areas in which such undertakings would not be feasible without supportive action. To accomplish its aim, TEDDY has focused on three different actions: (i) increasing awareness about the Paediatric Regulation revolution; (ii) reaching consensus on terms and instruments to be used for common research; and (iii) favoring close relationships among different stakeholders and partners from different EU Member States. After 3 years of activities, many results have been produced by the Network: surveys, databases, expert opinions, and recommendations. Linking together different stakeholders, including industry and patient associations, as well as academia and research centers, the Network has contributed to increasing awareness and participation in the Paediatric Regulation. In addition, many papers detailing original results have either been published or submitted for publication in peer-reviewed journals.

TEDDY is an original Network whose identity and role as a catalyzer of initiatives related to the use and development of pediatric drugs needs to be better clarified in the near future. Of particular importance is the need to reach consensus on best practices. The lack of a common view on pediatric research requirements among stakeholders across Member States remains the main challenge to be overcome.

The Task-force in Europe for Drug Development for the Young (TEDDY) is a Network of Excellence (NoE) funded under the Sixth European Commission (EC) Framework Programme for Research and Technological Development (FP6).[1] The project started in June 2005 and will run until 2010. It involves 19 partners from ten EU countries and also includes Israel.

To understand the objectives and actions of TEDDY, it is necessary to consider some of the characteristics of this research instrument. A NoE differs from other research instruments because it is not intended for a specific research theme, but for a whole research sector with the aim of sharing resources, permanently eliminating duplication of efforts, and promoting effective

use of resources. In particular, TEDDY must comply with the Second Call of the FP6: Life Sciences, Genomics, and Biotechnology for Health (LSH)-2003-1.2.1-1: Medicines for Children – Network of Excellence[2] requiring the structuring of efforts devoted to the development of medicines for children, by:

- covering all aspects involved;
- giving particular emphasis to the design of medicines for newborns and babies;
- developing close collaboration among academia, pharmaceutical industry, ethical bodies, and regulatory authorities.

To fulfill the aforementioned obligations, TEDDY set up a very complex and difficult-to-coordinate structure incorporating seven objectives and 12 Work-Packages. Life science-related topics such as pharmacogenomics, development and sex characteristics, and other pediatric medicines-related topics (drug availability, prescription of medicines to the pediatric population [aged 0–18 years], adverse drug reactions [ADRs], therapeutic needs, and research priorities) were included in the Network activities. Participants were asked to collaborate to enable a durable integration of their research capacities and knowledge.

This article discusses the role of and need for a European NoE in pediatric pharmacology with particular reference to the Paediatric Regulation approval and implementation processes.[3-5]

Activities and Main Results of the Task-force in Europe for Drug Development for the Young (TEDDY)

TEDDY activities have concentrated on life science and pediatric medicines-related topics, with the purpose of:

- stimulating the interaction of pediatric research groups on a multinational level;
- participating in the initiatives proposed by the European institutions to implement the new Paediatric Regulation.

The main results achieved are summarized below.

Pharmacogenomics/Pharmacogenetics

A review of the focus of published academic pediatric research in the EU has been performed. This unravelled the urgent need for confirmatory research to enable translation of potential pharmacogenetic findings into label recommendations.[6] Available expertise and commonly used methodology have been identified through a dedicated survey.[6] A methodologic initiative aimed at including pediatric pharmacogenomics and pharmacogenetics into the pediatric development process is ongoing.

Initiatives in this field (*ad hoc* Committee for Medicinal Products for Human Use [CHMP]/The European Medicines Agency [EMEA] Pharmacogenomics Working Party (PgWP) or the EMEA/Council for International Organizations of Medical Sciences [CIOMS]/the European Federation of Pharmaceutical Industries and Associations [EFPIA] guidelines) were not focused on pediatrics. Currently, a published inventory of pediatric pharmacogenomics/pharmacogenetics competencies exists and all interested parties (researchers, industry, regulatory bodies) can access it.[7]

Sex Issues

A bibliographic search on sex-related differences in the incidence and/or prevalence of specific diseases in childhood was completed.[8] The influence of sex on drug utilization and ADR rates and type was evaluated in selected drug classes. Results demonstrated that there is a difference in drug utilization according to sex, especially from adolescence on, and that the number of ADR reports was somewhat higher in boys than in girls and was mainly related to younger children. As of the age of 14 years, the number of reported ADRs was higher in girls than in boys. Researchers interested in pediatric sex issues were identified and asked to cooperate in future initiatives funded by the Seventh EC Framework Programme (FP7).

Before TEDDY, there were no initiatives in this field, despite the emphasis of the EC on the need to consider sex aspects in pediatric research.

Drug Prescription and Databases

The contents and main features of 18 prescription databases from ten EU countries have been characterized, enabling subsequent assessment of consistency and reliability for the purposes of pediatric research. Three prescription databases were used to produce reports and a publication.[9-22] Four additional European databases are being added to this research. Currently, prescription data on 5 million pediatric patients are available for use in common pharmacoepidemiologic studies. Differences by Anatomical Therapeutic Chemical classification, age, and countries in 244 267 ADR reports have been considered and submitted for publication.[23]

A two-stage, web-based Delphi survey was conducted among experts in Europe to develop common definitions for unlicensed and off-label drug use in children. Results were discussed with the EMEA before a final proposal was adopted. The definitions will be circulated within the scientific community and their adoption by relevant regulatory authorities will be recommended.[24]

Currently, pediatric prescription databases are few in Europe. In addition, no common standard methodology for the collection of data is currently adopted.

Pediatric Medicines Availability and Need

The European Pediatric Medicines Database (EPMD), including data on almost 600 medicines (centralized and decentralized), has been created.[25] Comparisons of drug availability, minimum approved age, price, and reimbursement system are available for selected groups of drugs and in selected countries.[26] Methodologic aspects of the existing pediatric trials (both for regulatory submission and nonregulatory purposes) evaluating the medicines in this database have been assessed, including a comparison between centralized/decentralized drugs, and the rate and type of trials for regulatory submission and nonregulatory purposes. An article on this is in preparation, as well as a position paper on the methodologic requirements for conducting clinical trials in children.

Proposals on priorities for pediatric research have been made based on the availability of pediatric data and according to the recommendations of the 14 TEDDY Therapeutic Experts Groups. An article with a specific focus on pediatric oncology has been published,[27] and others are in preparation. The availability of and need for pediatric orphan drugs has been investigated.

Before the introduction of the EU Paediatric Regulation, no similar activities were present within the European context. In addition to the information available from the European Clinical Trials[28] and EUDRAPharm Databases,[29] TEDDY could offer a compilation of relevant data for the EMEA and other stakeholders, which are not covered by the aforementioned systems.

Ethics

A survey investigating the ethical and legal context before and after the implementation of Directive 2001/20/EC (Clinical Trials Directive), [establishing provisions regarding the conduct of clinical trials on human subjects involving medicinal products, in particular relating to the implementation of good clinical practice], and encompassing 27 European countries was performed.[30] A questionnaire was used to measure consensus on initiatives aimed at implementing the recently approved EC recommendations[31] and a 'consensus position paper' is in preparation to be submitted to the EU regulatory body. Public discussions have been promoted to integrate the new pediatric rule in the current ethical and scientific debate on pediatric research and clinical trials involving children and to increase awareness on this sensitive topic.

The TEDDY survey anticipated other similar initiatives. The Network has demonstrated capacity in communicating with stakeholders, including Ethics Committees, and to scope out proposals with wider, international involvement. TEDDY endeavours to contribute to the current debate on ethical issues in pediatric clinical research with upcoming institutional initiatives.

The Future of the TEDDY Network

TEDDY represents a new entity in pediatric pharmaceutical research. It is different to a scientific society, a network for developing research or trials, or a consultative regulatory body. The ambition of TEDDY is to support existing pediatric networks, societies, and regulatory bodies to undertake novel initiatives, including those in areas where such undertakings would not be feasible without a supportive action.

According to the intrinsic nature of a NoE, TEDDY has been requested to demonstrate its sustainability once the financial support expires. To do this, we are focusing on actions aimed at the following:

1. Promoting collaboration within pediatric societies and academia to engage in concerted efforts to achieve wider EU-supported objectives, and promoting specific networking and pediatric research. This is particularly relevant for Small and Medium Enterprises (SMEs), which lack expert advice and guidance in this field.
2. Creating consensus on terms and instruments to be used for pediatric research by organizing expert meetings and publishing position papers on known bottlenecks in pediatric drug development and use.
3. Favoring friendly relationships among partners as well as with interested parties and authorities. While collaboration with partners, firms, and professional and patient associations is increasing and new initiatives are including new Member States and new research groups, collaboration with European and National Regulatory Agencies and Health Institutions is scarce.

Conclusions

Full implementation of policies and strategies for medicines for children is a long-term effort that justifies the need for a cohesive element to ensure effective cooperation between stakeholders. This very need constitutes a good reason for the TEDDY Network to continue beyond its funded period. The first 3 years of the Network activities have been favourable in terms of durable collaborations, and unraveling opportunities for original scientific research and innovative medicinal products.

More focus and efforts are required to achieve sustainability. In particular, the Network should better clarify its identity as a catalyzer of research activities between relevant networks. Of particular importance is the need to reach consensus on best practices. The lack of a common view on pediatric research requirements among stakeholders across Member States remains the main challenge to be overcome.

Finally, a more friendly relationship with European and National Regulatory Agencies and Health Institutions should be promoted in order to make better use of TEDDY resources and results.

Acknowledgments

This paper is part of the TEDDY Network of Excellence funded within the Sixth EC Framework Programme (Contract no. 0005216 LSHBCT-2005-005126). Oscar Della Pasqua is the partner of the Network, Leader of Work-Package 2. Carlo Giaquinto has received consultancies from GlaxoSmithKline (GSK), Abbott, BMS, Tibotec, Gilead, Sanofi Pasteur MSD (SPMSD), and Boehringer Ingelheim (BI) and honoraria from GSK, Abbott, BI, Tibotec, and SPMSD. The other authors have no conflicts of interest that are directly relevant to the content of this paper.

References

1. European Commission. Sixth EU Framework Programme (FP6) [online]. Available from URL: http://ec.europa.eu/research/fp6/ [Accessed 2008 Dec 8]
2. European Commission. Work programme for the specific programme for research, technological development and demonstration: "integrating and strengthening the European research area". PRIORITY 1: Life Sciences, Genomics and Biotechnology for Health, the Sixth Framework Programme [online]. Available from URL: http://cordis.europa.eu/fp6/ [Accessed 2008 Jul 9]
3. European Commission Enterprise Directorate General. Better medicines for children: proposed regulatory actions on paediatric medicinal products. Consultation document [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2002/feb/cd_pediatrics_en/pdf [Accessed 2008 Jul 9]
4. Regulation (EC) n. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. J Eur Union 2006; L378: 1-19
5. Regulation (EC) n. 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use. J Eur Union 2006; L378: 20-1
6. Krekels EH, van den Anker JN, Baiardi P, et al. Pharmacogenetics and paediatric drug development: issues and consequences to labelling and dosing recommendations. Expert Opin Pharmacother 2007 Aug; 8 (12): 1787-99
7. Krekels E, Ceci A, Iolascon A, et al. The role of paediatric pharmacogenetic studies in Europe. Pharm Policy Law. In press
8. Grosch-Woerner I, Verhamme K, Kagedal B, et al. Recommendations on gender issues in clinical research management [online]. Available from URL: http://www.teddyoung.org [Accessed 2008 Jul 9]
9. Sen EF, Sturkenboom MCJM. The TEDDY Network: epidemiological trends in paediatric drug use in Europe. EJHP 2007 (6): 22-4
10. Ackers R, Murray ML, Besag FM, et al. Prioritizing children's medicines for research: a pharmacoepidemiologic study of antiepileptic drugs. Br J Clin 2007 Jun; 63 (6): 689-97
11. Medina Claros AF, Mellado Peña MJ, y Baquero Artigao F. Bases para el uso clínico de fármacos en niños: situación actual de uso de farmacos pediatricos en España. An Esp Ped Formación Continuada 2008; 6 (3): 187-90
12. Neubert A, Sturkemboon MCJM, Murray ML, et al. Databases for paediatric medicines research in Europe: assessment and critical appraisal. Pharmacoepidemiol Drug Saf. Epub 2008 Oct 31
13. Sturkemboon MCJM, Verhamme KMC, Nicolosi A, et al. Drug use in children: cohort study in three European countries. BMJ 2008 Nov 24; 337: a2245
14. Sturkenboom M, Felisi M, Manfredi C, et al. Paediatric status and off-label use of drugs in children in Italy, United Kingdom and The Netherlands. Pharm Policy Law. In press
15. Sturkenboom M, Verhamme K, Murray M, et al. General drug utilization in children: a multinational database study in the TEDDY Project [poster]. 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 2007 Aug 19-22; Quebec City (QC)
16. Neubert A, Murray M, Sturkenboom M, et al. Population-based databases for paediatric medicine research in Europe: a TEDDY appraisal [poster]. 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 2007 Aug 19-22; Quebec City (QC)
17. Verhamme K, Picelli G, Giaquinto C, et al. Cardiovascular drug use in children: the Teddy Project [poster]. 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 2007 Aug 19-22; Quebec City (QC)
18. Murray M, Neubert A, Picelli G, et al. Drug utilisation of neuropsychiatric drugs in children: a multinational study within the TEDDY project [poster]. 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 2007 Aug 19-22; Quebec City (QC)
19. Sturkenboom M, Verhamme K, Murray M, et al. Respiratory drug use in children: a multinational database study in the TEDDY project [poster]. 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 2007 Aug 19-22; Quebec City (QC)
20. Neubert A, Murray M, Sturkenboom M, et al. Drug utilisation of analgesics and anti-inflammatory drugs in children: a multinational database study within the TEDDY project [poster]. 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 2007 Aug 19-22; Quebec City (QC)
21. Felisi M, Baiardi P, Verhamme K, et al. Paediatric status and off-label use of drugs in children [oral presentation]. 11th Biannual European Society for Developmental Parinatal and Paediatric Pharmacology Congress; 2008 Jun 4-7; Rotterdam
22. Sen EF, Verhamme K, Neubert A, et al. Respiratory drug use in children in the Netherlands, Italy and United Kingdom [oral presentation]. 11th Biannual European Society for Developmental Parinatal and Paediatric Pharmacology Congress; 2008 Jun 4-7; Rotterdam
23. Verhamme K, Elferink-Stinkens P, Murray M, et al. Adverse drug reaction reporting in children: the Teddy project [poster]. 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management; 2007 Aug 19-22; Quebec City (QC)
24. Neubert A, Bonifazi A, Catapano M, et al. Defining off-label and unlicensed use of medicines for children: results of a Delphi survey. Pharmacol Res. In press
25. Ceci A, Felisi M, Baiardi P, et al. Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years. Eur J Clin Pharmacol 2006; 62 (11): 947-52
26. Task-force in Europe for Drug Development for the Young (TEDDY) [online]. Available from URL: http://www.teddyoung.org [Accessed 2008 Dec 8]
27. Paolucci P, Pritchard Jones K, del Carmen Cano Garcinuno M, et al. Challenges in prescribing drugs for children with cancer. Lancet Oncol 2008 Feb; 9 (II): 176-83
28. European Clinical Trials Database (EudraCT) [online]. Available from URL: http://eudract.emea.europa.eu/ [Accessed 2008 Dec 8]
29. Community Database on Medicinal Products (EUDRAPharm) [online]. Available from URL: http://eudrapharm.eu/eudrapharm/welcome.do [Accessed 2008 Dec 15]
30. Altavilla A, Giaquinto C, Giocanti D, et al. Activity of ethics committees in Europe on issues related to clinical trials in paediatrics: results of a survey. Pharm Policy Law. In press
31. European Commission Enterprise Directorate General. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population: recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use [online]. Available from URL: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev10.htm [Accessed 2008 Nov 25]

Correspondence: *Adriana Ceci*, Consorzio per Valutazioni Biologiche e Farmacologiche, Via Palestro, 26 27100 Pavia, Italy.
E-mail: adriana.ceci@teddynoe.org