

The European Union Pediatric legislation: impact on pharmaceutical research in pediatric populations

The first European Paediatric Regulation came into force in the European Union on the 26 January 2007. A few years later, its impact on pharmaceutical research starts to be assessed from different perspectives. Such reflection process is quite valuable as it is anticipated that this regulation will be revised in a few years. Major achievements have occurred and have been acknowledged but there are also divergent opinions, and questions or concerns have been expressed, sometimes leading to interesting controversies. This article will review some background and key features of the European Paediatric Regulation and present, through the examples of pediatric psychopharmacology and oncology, its impact on pharmaceutical research with suggestions for future of pediatric research.

Keywords: child psychopharmacology • ethics • pediatric drug development • pediatric regulation

Following a longer history of pediatric drug legislation in the US, the first European Paediatric Regulation came into force in the European Union (EU) on the 26 January 2007 [1]. This legislation brought faster and more dramatic changes in Europe than the ones that occurred in the USA. Before its potential revision, its impact started to be assessed from different perspectives.

Major achievements have occurred and have been acknowledged, for instance in the EU Commission's 2013 report [2], but there are also divergent opinions, and questions or concerns have been expressed sometimes leading to controversies.

The pediatric population is extremely heterogeneous from neonates and to adolescents with major developmental cognitive and physiological changes ending with puberty and significant differences in pharmacodynamics and pharmacokinetics; these developmental aspects are out of the scope of this review but should never be forgotten.

Pediatric regulations

Toward a global regulatory consensus

It is beyond any reasonable doubt that the

need to obtain specific information for medicines used in pediatric population and the urge to develop innovating drugs for children is reaching a consensus on a global basis. If the USA paved the way for legislation aimed at producing drugs for children, followed more recently by the EU, further initiatives or pediatric considerations are taking place globally as evidenced for instance by the circular that the Chinese Government released in May 2014 on ensuring drug safety for children, raising requirements in various aspects such as research and development, supply and quality management [3].

Pediatric development is heavily controlled by regulations. But regulations do not suffice. It is of paramount importance to ensure that pediatric development is scientifically and ethically sound, and it is not uncommon to notice that ethics committees may have different opinions about a program agreed with the US or EU health authorities.

Reviewing the successes and the omissions of the US FDA pediatric exclusivity incentive, and after showing that the pediatric clinical drug testing legislation originates almost 200 years ago, that is, from the XIX

Philippe Auby

Global Clinical Research, Paediatric Neuro-Psychiatry, Lundbeck SAS, 37-45, Quai du Président Roosevelt, 92445 Issy-les-Moulineaux Cedex, France
phia@lundbeck.com

FUTURE
SCIENCE

part of

fsg

century, with the creation of the AMA Women and Children's Division and the American Academy of Pediatrics, Rivera & Hartzema remind us that 'pediatric drug development is guided by public policy and has a long history of successes and failures' [4]. As an example, they consider the National Childhood Vaccine Injury Act of 1986 as one of the reasons enabling vaccine development to continue, by creating in 1988 the National Vaccine Injury Compensation Program (VICP); this VICP was established to ensure an adequate supply of vaccines, stabilize vaccine costs, and establish and maintain an accessible and efficient forum for individuals found to be injured by certain vaccines [5]. It is important to note that to support VICP mission, research was also performed to answer the question about the possible link between vaccines and autism; several reports confirmed that there was the MMR (measles–mumps–rubella) vaccine is not associated with the onset of autism in children as reported and confirmed by Maglione *et al.* [6].

A pediatric milestone occurred in 1994, when the USA implemented the 'Pediatric Labeling Rule' which paved the way for legislation aimed at producing drugs for children. This initiative was followed in 1997 by the FDA Modernization Act that 'provided an incentive for pharmaceutical companies to study products for which there would be a health benefit in the pediatric population' [7]. This created a 'voluntary process where FDA would define the products which needed pediatric studies, outline the necessary studies and issue sponsors a Pediatric Written Request'. Pharmaceutical companies could choose to respond or not to the Pediatric Written Request, and if responding positively six additional months of marketing exclusivity were received upon completion of the agreed program. This process is considered as the key main legislative initiative that has changed pediatric drug development in the USA. In 2012, the FDA Safety and Innovation Act, signed into law on July 9 2012, expanded the FDA's authorities and strengthened the agency's ability to safeguard and advance public health, including the fact that the pediatric regulation became permanent [8].

The EU Paediatric Regulation

In Europe, a similar 'pediatric' reflection process started in the late nineties, following the US initiatives, and in December 2000, the European Health Council asked the commission to take specific actions to remedy the fact that the majority of medicines used in children have never been tested for this specific population; this concern had been raised by regulators, individual member states, members of the European Parliament, pediatricians and importantly

also by parents' representatives. The consultation paper released in 2002 called 'Better Medicines for Children' presented the European Commission reflections and positions for regulatory ambitious actions on pediatric medicines which were used to build the future EU pediatric regulation [9] in order to bring faster and more profound changes in EU compared with USA. It is in this consultation paper that was emphasized that despite representing 20% of the total population in the EU, the pediatric populations were 'therapeutic orphans' as the majority of medicines were still only developed and assessed for adults with an estimation that up to 90% of medicinal products, depending on therapeutic areas, used in younger patients have never been specifically evaluated for such use.

The European Paediatric Regulation came into force in EU on the 26 January 2007 [1]. Its core objective is 'to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0–17 years, ensuring that medicines for use in children are of high quality, ethically researched and authorized appropriately'; part of it is also to facilitate the availability of information on the use of medicines for children. Of course for political reasons, the regulation aimed solely to improve the health of European children, but the reality is quite different as clinical trials nowadays are rather global than solely European; because of the lack of patients and the need to lower cost of research, global clinical trials are now the rule, not only speeding the recruitment but also offering huge advantages for some host countries, by potentially enhancing their local economies, improving personal trainings and ultimately improving patient care.

Like the US pediatric regulation, the ultimate goal of the EU regulation is to improve children's health through advancements in research within a new framework for evaluating the efficacy and safety of medicines for children. But unlike in the USA, pediatric development became mandatory in EU for all new medicinal products in development unless a waiver is granted, and pharmaceutical companies have to send a Pediatric Investigation Plan (PIP) as early as the end of pharmacokinetic studies in adults and pediatric discussions may defer or even block the registration of a new drug for adult patients. A PIP reflects the development plan on clinical, nonclinical and technical aspects including timelines and covers all existing (adult) indications, dosage forms and new indications. Submissions for new market authorizations are only accepted if the package contains pediatric data according to the pre-agreed PIP or a letter of granted deferral or waiver.

Child & adolescent psychiatry

In May 2014, WHO's 'Health for the World's Adolescents' report reveals that 'depression is the predominant cause of illness and disability for both boys and girls aged 10–19 years' and adds that the 'top three causes of adolescent deaths globally are road traffic injuries, HIV/AIDS and suicide. Worldwide, an estimated 1.3 million adolescents died in 2012' [10]. Depression is far from being uncommon in children and adolescents, as the prevalence of major depressive disorder (MDD) is estimated to be approximately 2% in children and 4–8% in adolescents, with a male-to-female ratio of 1:1 during childhood and 1:2 during adolescence [11].

Limited pediatric data & research in psychopharmacology

Despite the fact that it is widely recognized that mental disorders in children and adolescents lead to a major burden for them and for their families, some facts are troublesome, such as the obvious imbalance between the available armamentum in adult psychopharmacology compared with child and adolescent psychiatry or the discrepancy between the increased use of psychotropic agents in pediatric population and the rather lack of solid scientific supportive data.

Assessing pediatric research in neuropsychiatry by measuring the proportion of pediatric studies registered in ClinicalTrials.gov between 2006 and 2011 for new products or new indications, Murthy *et al.* [12] confirmed that only a small proportion of studies are performed in pediatric population with significant differences between disorders as 'this deficiency is most pronounced for depression and schizophrenia'.

Antidepressant & antipsychotic recent pediatric developments

Antidepressant and antipsychotic development examples will be used to illustrate the expected impact on the EU pediatric legislation on child and adolescent psychiatry and clinical psychopharmacological research with minors.

Antidepressants in child & adolescent psychiatry

In Europe, only one antidepressant, fluoxetine, a selective serotonin uptake inhibitor (SSRI), is approved for the treatment of pediatric MDD, while significantly more agents are approved for use in adults, for instance up to 23 in France (Table 1) [13].

The American Academy of Child and Adolescent Psychiatry recommends for children and adolescents who do not respond to supportive psychotherapy or who have more complicated depressions a trial with specific types of psychotherapy and/or antidepressants

('recommendation 9') and reports that more severe depressive episodes will generally require treatment with antidepressants; they add that antidepressants may be administered alone until the child is amenable to psychotherapy or, if appropriate, they can be combined with psychotherapy from the beginning of treatment [14]. In Europe, for instance the National Institute for Clinical Excellence (NICE) MDD Guideline states that antidepressant treatment should not be used for the initial treatment of children and adolescents with mild depression, and should only be used in case of moderate to severe depression in combination with a concurrent psychological therapy [15].

In practice in EU, antidepressants, mainly SSRIs, are commonly prescribed in children and adolescents for depression [16], despite fluoxetine being the only authorized drug for this indication. If tricyclic antidepressants are not useful in treating depression in prepubertal children, and may have a moderate effect at best in adolescents [17], the use of SSRIs remains based on quite few positive efficacy results to date.

The reasons why many of the efficacy studies of antidepressants in pediatric MDD have failed are quite diverse [18], multiple and still putative, from potential age-related differences in pharmacokinetics and pharmacodynamics, methodological flaws (with regard to patient recruitment, study design, lack of dose finding studies or correlation between greater placebo response and high number of study sites) to high placebo response in pediatric depression [19]. Identifying evidence-based dosing strategies is a key initial step in pediatric programs with pediatric pharmacokinetic studies providing important information regarding how best to dose drugs in efficacy studies [20]. This has actually been emphasized in the EMEA Generalized Anxiety Disorder guideline, in which it is stated that studies in the pediatric patient population should be supported by adequate pharmacokinetic studies [21].

Although some of the antidepressants may not be beneficial (like the tricyclics [17]), the current evidence of their proven therapeutic benefit is inadequate to guide best practice and these failures contrast with clinical practice as child and adolescent psychiatrists, like

Table 1. Antidepressants approved for use in France.

	Adult	Pediatric
Number of antidepressants approved for use	23	1
– Tricyclics	8	0
– SSRIs	6	1 = fluoxetine
– Others	8	0

SSRI: Selective serotonin uptake inhibitor.

all pediatricians using drugs off-label, are prescribing SSRIs as the first-line pharmacologic treatment.

The recently published inconclusive duloxetine studies [22,23], as neither the investigational drug (duloxetine) nor the active control (fluoxetine) separated from placebo at the 10-week end point, illustrate the difficulty to conduct pediatric MDD studies and emphasize the high rate of placebo response in this indication, especially as fluoxetine always demonstrated robust evidence of efficacy in pediatric MDD. Rutherford and Rose [24] reviewing the factors influencing placebo response by assessing evidence from the published adult literature concluded that there are four design features associated with the strongest evidence of influence on placebo response: number of sites, quality of rater blinding, number of treatment arms and probability of receiving placebo. Similarly, Bridge *et al.* reported in 2009 that for pediatric MDD studies, the best predictor of the proportion of patients responding to placebo was the number of study sites [19].

Therefore, classical study designs that have been used previously and that have failed should be questioned and innovative study designs should be explored, like for instance the sequential parallel comparison design (SPCD) proposed by Fava *et al.* in 2003. The SPCD consists of two phases of equal duration, with 6 weeks representing a common choice. In recent years, SPCD trials have utilized the following two-phase format: unequal randomization is applied between active drug and placebo, with more subjects allocated to placebo; then, at the end of the first phase, placebo nonresponders are re-randomized usually with an equal allocation to placebo or active drug. This design enables to reduce the number of arms and limit the sample size, therefore the number of sites, and the probability and expectation of receiving placebo [25].

The EMA Guideline on clinical investigation of medicinal products in the treatment of depression published in 2013 [26] states that for children and adolescents, “efficacy in acute treatment should be demonstrated in at least one short-term trial of 8 weeks duration (or longer) including a placebo and an active comparator arm. In earlier clinical trials with careful patient selection resulting in a homogeneous patient population a study duration of 8 weeks has been shown sufficient for statistically significant and clinically meaningful separation of active treatment from placebo. If longer study durations are implemented, this should be justified in the protocol and must be balanced against the longer use of placebo control.” The study duration is indeed an important design feature as minimizing the placebo exposure in pediatric patients is ethically and scientifically sound.

There is nowadays limited research in the field of pediatric MDD and only two agreed PIPs for antidepressants are published on the EMA website [27]. Little information about study design is available on the EMA website, but given the inconclusive duloxetine trials, pediatric MDD efficacy studies should choose a different design than these two duloxetine trials.

Consequently, enabling and promoting innovative designs resulting in conclusive trials should indeed be an accurate way to assess the impact of EU and US pediatric legislations on pharmaceutical research in pediatric population.

Pediatric development of antipsychotics

Triggered by the US pediatric regulation, numerous well-designed efficacy studies have been performed in children and adolescents with psychotic or bipolar disorders leading to a different picture than for antidepressants. With the more recent influence of EU pediatric regulation the number of clinical studies of antipsychotics in pediatric patients will continue to increase. Table 2 summarizes the completed or agreed pediatric development plans for the second-generation antipsychotics (SGAs) according to the available information on the FDA and EMA websites.

In 2011, Fraguas *et al.* [28] conducted a ‘comprehensive review of the data from controlled and uncontrolled prospective studies in children and adolescents with psychotic and bipolar disorder spectrum disorders’ comparing efficacy and tolerability of SGAs, either head-to-head, against a first-generation antipsychotic, or against placebo. Such review is needed as despite the increased knowledge about the use of antipsychotics in pediatric populations, little is known about their comparative efficacy when compared with the adult literature and numerous questions and true concerns have been raised about their safety and tolerability urging new research [29]. Their review included 34 studies which have enrolled 2719 children and adolescents and confirmed that, “as in adults, SGAs are not a homogeneous group in children and adolescents with psychotic and mood disorders. However, also as in adults, except for superior efficacy with clozapine, the heterogeneity within the SGA group is mainly limited to differences in the rates and severity of adverse events”.

Interestingly, all but one pediatric developments are performed for new or on-patent drugs. For off-patent drugs, the EU regulation created a new marketing authorization, the PUMA (Paediatric Use Marketing Authorization), which provides 10 years of data protection for pediatric innovation. To date, within the antipsychotic area we are assessing, only one program, the PERS (Paediatric European Risperidone Studies),

is evaluating a drug that is off-patent [30]. This is in line with the EU Commission's 2013 report qualifying the PUMA initiative as a disappointment [2].

At the moment, placebo-controlled trials continue to be a kind of gold standard for these pediatric programs, required or recommended in schizophrenia research, but the scientific and ethical rationale of use of placebo is more and more questionable. Emsley and Fleischhacker, in 2013, systematically reviewed the published relapse-prevention placebo-controlled with SGAs in schizophrenia, thoroughly assessed the use of placebo in this context and wondered if its use was still justified [31]. They concluded that alternative designs would be welcome and made some methodological suggestions. Like for adult patients with schizophrenia, adolescent psychiatry lacks studies investigating the consequences of relapse for adolescent patients with schizophrenia, but the question is extremely valid.

Given the fact that due to the enforcement of pediatric regulations, more valuable information about the use of SGAs in adolescents with schizophrenia is available, it is time to wonder if the use of placebo is still acceptable in a clinical trial. And if still scientifically justified, how long can its use be ethically accepted?

Therefore it is vital to maintain open dialog between regulatory authorities, health professionals, pharmaceutical companies and society as a whole in order to prevent what some authors call 'perverse incentives' of the pediatric regulations [32].

Controversies in pediatrics

In 2012, Saint-Raymond and Herold published a paper questioning the failure to deliver drugs for pediatric cancers [33]; in most pediatric areas, with the main exceptions in rheumatology and oncology, the diseases affecting children are close to those affecting adults with respect to type of diseases and pathophysiology [33]. The EU pediatric regulation, as clarified in July 2012 by the policy on the determination of the condition(s) for a PIP/Waiver [34], links indications and conditions, and the Medical Dictionary for Regulatory Activities should be used as guidance.

However, in pediatric rheumatology and oncology, conditions under study in adults may not have a pediatric correlate.

The impact of both US and EU pediatric regulations has been positive in pediatric rheumatology according to Ruperto *et al.* [35], with the EU regulation having favored the development of new treatments for children with juvenile idiopathic arthritis.

The situation is much more controversial for pediatric oncology, with some authors considering that unintended problems (referring to exaggerated

Table 2. Recent pediatric developments of antipsychotics.

	EU	US
Asenapine	Yes	Yes
Aripiprazole	Yes	Yes
Risperidone	PUMA	Yes
Paliperidone	Yes	Yes
Olanzapine	No	Yes
Quetiapine	No	Yes
Loxapine	Yes	?
Clozapine	No	No
Ziprasidone	No	Yes
lloperidone	Waiver	Yes
Lurasidone	Yes	Yes
LY2140023 (discontinued)	Yes	No
OPC-34712	Yes	Yes
Bitopertin	Yes	?
ABT-126	Yes	?

PUMA: Paediatric Use Marketing Authorisation

assumptions about the frequency of childhood cancers and feasibility of the proposed clinical trials) have been created in this field [36] and others, like the Institute of Cancer Research in London, urging the EU to change the law as children are "denied life-saving drugs by current rules" [37]; although waivers are appropriate when a drug is not anticipated to work in childhood cancers, they are often granted even when evidence shows that a drug for adult cancers has a 'mechanism of action' that could treat childhood cancers too [38]. In the USA, more than 90% of children and adolescents diagnosed with cancer are enrolled at Children's Oncology Group institutions into clinical trials, a higher proportion than adults diagnosed with cancer [38].

This debate puts emphasis on two basic questions, the challenging feasibility issues of pediatric recruitment and the appealing possibility to analyze the mechanism of action and target of the new medicines in order to eventually obtain the necessary data in children within a reasonable timeframe.

Conclusion & future perspective

The European Paediatric Regulation is a major society achievement opening a new era of European drug regulatory history. Its consequences start to be visible on pharmaceutical research. Together with the US legislation, that is now permanent, both regulations should further consolidate a strict regulatory framework in order to improve children's health.

It is of paramount importance to thoroughly assess their impact and to ensure the highest scientific and ethical standards in worldwide pediatric development.

As put in inspirational perspective by Weaver and Hendrick, we can learn from the past and apply Mandela's memory toward a global pediatric future [39]:

“There can be no keener revelation of a society's soul than the way in which it treats its children ... Our actions and policies, and the institutions we create, should be eloquent with care, respect and love. This is essentially a national task. The primary responsibility is that of government, institutions and organized sectors of civil society. But at the same time we are all

of us, as individuals, called upon to give direction and impetus to the changes that must come.”

– Speech by President Nelson Mandela, Mahlabla Ndlopfu, Pretoria, South Africa on 8 May 1995.

Financial & competing interests disclosure

Philippe Auby is a Lundbeck employee. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- The European Paediatric Regulation came into force on the 26 January 2007 opening a new era of European drug regulatory history.
- The EU Paediatric Regulation, like its USA counterpart, is changing pediatric development for the more recent products but has still little impact for off-label drugs.
- Like what happened in the US, the impact of the pediatric legislation needs to be assessed before its potential revision in the next coming years; significant achievements already occurred but there are also questions or concerns sometimes leading to interesting controversies.
- Despite the fact that mental disorders in children and adolescents lead to a major burden for them and for their families, there is an obvious imbalance between the available armamentum in adult compared with child and adolescent psychiatry.
- There are specific challenges associated to studying drugs in pediatric population, for instance a majority of studies of antidepressants in pediatric major depressive disorder have failed to bring conclusive date, therefore urging to develop new and innovative study designs.
- Placebo-controlled trials considered as the gold standard even in schizophrenia research may become more and more questionable and alternative designs will have to be developed.
- It is vital to maintain open dialogue between regulatory authorities, health professionals, pharmaceutical companies and society as a whole in order to prevent 'perverse incentives' of the pediatric regulations.

References

- 1 European Commission. Regulation (EC) No 1901/2006 of the European Parliament and of the council on medicinal products for paediatric use (2006). http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf
- 2 European Union Commission 2013 Better Medicines for Children. From concept to reality. Progress report on the paediatric regulation (EC) No 1901/2006 COM 443 (2013). [http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com\(2013\)443_en.pdf](http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf)
- 3 China Enhances Drug Safety For Children. <http://english.cntv.cn/2014/05/30/ARTI1401455017142544.shtml>
- 4 Rivera DR, Hartzema AG. Pediatric exclusivity: evolving legislation and novel complexities within pediatric therapeutic development. *Ann. Pharmacother.* 48(3), 369–379 (2014).
- 5 National Vaccine Injury Compensation Program (VICP) 1988. www.hrsa.gov/vaccinecompensation/index.html
- 6 Maglione MA, Das L, Raaen L *et al.* Safety of vaccines used for routine immunization of US children: a systematic review. *Pediatrics* 134(2), 325–337 (2014).
- 7 Murphy D. Pediatric drug development: What have we learned? Workshop 3: addressing the barriers to pediatric drug development. *Institute of Medicine*, June 2006, Washington DC, USA.
- 8 US FDA Safety and Innovation Act (FDASIA) (2012). www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentsstotheFDCA/FDASIA
- 9 Better medicines for Children. Proposed regulatory actions on Paediatric medicinal products. Consultation document. (2002). http://ec.europa.eu/health/files/pharmacos/docs/doc2002/feb/cd_paediatrics_en.pdf
- 10 World Health Organization (WHO). WHO, “Health for the world's adolescents”. www.who.int/mediacentre/news/releases/2014/focus-adolescent-health
- 11 Birmaher B, Ryan ND, Williamson DE *et al.* Childhood and adolescent depression: a review of the past 10 years.

- Part I. *J. Am. Acad. Child Adolesc. Psychiatry* 35, 1427–1439 (1996).
- 12 Murthy S, Mandl KD, Bourgeois F. Analysis of pediatric clinical drug trials for neuropsychiatric conditions. *Pediatrics* 131(6), 1125–1131 (2013).
 - 13 *Vidal Le Dictionnaire (90th Edition)*. French and European Publications Inc., (2014).
 - 14 Birmaher B, Brent D, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J. Am. Acad. Child Adolesc. Psychiatry* 46, 1503–1526 (2007).
 - 15 National clinical practice guideline 28. The British Psychological Society & the Royal College of Psychiatrists. (2005 & 2013). www.bps.org.uk/publications/policy-and-guidelines/practice-guidelines-policy-documents/practice-guidelines-poli
 - 16 Moreno C, Arango C, Parellada M, Shaffer D, Bird H. Antidepressants in child and adolescent depression: where are the bugs? *Acta Psychiatr. Scand.* 115, 184–195 (2007).
 - 17 Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Syst. Rev.* 18, 6 (2013).
 - 18 Emslie GJ, Ryan ND, Wagner KD. Major depressive disorder in children and adolescents: clinical trial design and antidepressant efficacy. *J. Clin. Psychiatry* 66(Suppl. 7), 14–20 (2005).
 - 19 Bridge JA, Birmaher B, Iyengar S, Barbe RP, Brent DA. Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *Am. J. Psychiatry* 166(1), 42–49 (2009).
 - 20 Findling RL, McNamara NK, Stansbrey RJ *et al.* The relevance of pharmacokinetic studies in designing efficacy trials in juvenile major depression. *J. Child Adolesc. Psychopharmacol.* 16, 131–145 (2006).
 - 21 Guideline on the clinical investigation of medicinal products indicated for Generalized Anxiety Disorder. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003510.pdf
 - 22 Atkinson SD, Prakash A, Zhang Q *et al.* A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorders. *J. Child Adolesc. Psychopharmacol.* 24(4), 180–189 (2014).
 - 23 Emslie GJ, Prakash A, Zhang Q, Pangallo BA, Bangs ME, March JS. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorders. *J. Child Adolesc. Psychopharmacol.* 24(4), 170–179 (2014).
 - 24 Rutherford BR, Roose SP. A model of placebo response in antidepressant clinical trials. *Am. J. Psychiatry* 170, 723–733 (2013).
 - 25 Doros G, Pencina M, Rybin D, Meisner A, Fava M. A repeated measures model for analysis of continuous outcome in sequential parallel comparison design studies. *Stat. Med.* 32(16), 2767–2789 (2013).
 - 26 Guideline on clinical investigation of medicinal products in the treatment of depression. (2013). EMA/CHMP/185423/2010 Rev. 2. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143770.pdf
 - 27 EMA. Opinions and decisions on paediatric investigation plans. www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp
 - 28 Fraguas D, Correll CU, Merchan-Naranjo J *et al.* Efficacy and safety of second-generation antipsychotics in children and adolescents with psychotic and bipolar spectrum disorders: comprehensive review of prospective head-to-head and placebo-controlled comparisons. *Eur. Neuropsychopharmacol.* 21, 621–645 (2011).
 - 29 Menard ML, Thümmel S, Auby P, Askenazy F. Preliminary and ongoing French multicenter prospective naturalistic study of adverse events of antipsychotic treatment in naive children and adolescents. *Child Adolesc. Psychiatry Ment. Health* 8(18) (2014).
 - 30 Paediatric European Risperidone Studies (PERS). www.pers-project.com
 - 31 Emsley R, Fleischhacker W. Is the ongoing use of placebo in relapse-prevention clinical trials in schizophrenia justified? *Schizophr. Res.* 150, 427–433 (2013).
 - 32 Gaifulina R. Regulation and paediatric drug trials: patents, plans, and perverse incentives. *Res. Ethics* 7(2), 51–57 (2011).
 - 33 Saint-Raymond A, Herold R. Medicines for pediatric oncology: can we overcome the failure to deliver? *Expert Rev. Clin. Pharmacol.* 5(5), 493–495 (2012).
 - 34 EMA Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (Scope of PIP/waiver). www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf
 - 35 Ruperto N, Vesely R, Saint-Raymond A, Martini A, for or the Paediatric Rheumatology International Trials Organisation (PRINTO). Impact of the European paediatric legislation in paediatric rheumatology: past, present and future. *Ann. Rheum. Dis.* 72, 1893–1896 (2013).
 - 36 Rose K. European Union Pediatric legislation jeopardizes worldwide, timely future advances in the care of children with cancer. *Clin. Ther.* 36(2), 163–177 (2014).
 - 37 Children's Oncology Group. <http://cog-foundation.org>
 - 38 Breaking down the barriers to treating childhood cancer. www.icr.ac.uk/press/recent_featured_articles/childhood_cancer_barriers/index.shtml
 - 39 Weaver MS, Hendricks M. Historical perspective: a president who prioritized children: applying Mandela's memory toward a global pediatric oncology future. *Pediatr. Blood Cancer* 61, 1145–1146 (2014).