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PEDIATRIC FUNGAL INFECTIONS (T LEHRNBECHER, SECTION EDITOR)

The Changing Landscape for Paediatric Regulation of Pharmaceutical Agents with a Focus on Antifungal Agents

Brian T. Fisher [1,2]

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Abstract The limited paediatric specific data for pharmaceutical agents has been a persistent issue for over a century. Since the late 1990s, two of the world's largest regulatory agencies, the Food and Drug Administration and the European Medicines Agency, have made concerted efforts backed by federal legislation aimed to improve the availability of paediatric data for many pharmaceutical agents. In the same time frame, there has been considerable research and development of new antifungal agents to help combat life-threatening invasive fungal disease. The evolving landscape of pharmaceutical regulation has helped to establish paediatric appropriate dosing recommendations for a number of these antifungal agents. However, the process by which paediatric data are realized is still too slow often leaving years between the initial adult approved indication and subsequent paediatric indications. This delay in paediatric data continues to perpetuate off-label use of many antifungal therapies in children, which can have negative consequences. As we strive to improve the availability of paediatric data for pharmaceutical agents, there needs to be a focus on timely delivery of these data to eliminate the window between adult and paediatric indications.

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✉ Brian T. Fisher
fisherbria@email.chop.edu

[1] Division of Infectious Diseases and the Center for Paediatric Clinical Effectiveness, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

[2] Center for Clinical Epidemiology and Biostatistics Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

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Introduction

Invasive fungal disease (IFD) is a potential source of significant morbidity and mortality among children with complex medical problems, including children with a primary, acquired, or iatrogenic immunocompromised state. Furthermore, this population of children at risk for IFD appears to be growing given the increased frequency of interventions such as transplantation and increase in the availability and indications for a variety of immunomodulatory agents [1–4].

Fortunately, commensurate with the increase in the population at risk for IFD is an increase in the number of antifungal agents developed for the treatment of these infections. From the time that amphotericin B was discovered in the mid-1950s, there was a near absence of antifungal development in the ensuing 35 years. Since 1990, numerous azoles, echinocandins, and lipid formulation amphotericin products have been researched, developed, and brought to the market [5]. Once these agents are available, the clinician caring for adult patients can begin to administer these agents informed by recommendations for dosing and estimates of potential side effects based on pre-marketing studies.

This is not the case for clinicians caring for paediatric patients at risk for or suffering from an IFD. Instead, paediatric clinicians are left to decide between the lesser of two evils, use an older agent that may be less effective but that may have information on paediatric specific dosing and adverse event rates or to administer a newly approved antifungal agent guided only by data extrapolated from adult studies. When clinicians choose the latter, they often struggle to ensure insurance

coverage and there is significant potential for under or over dosing the medication.

This clinical conundrum is well recognized by various agencies governing pharmaceutical regulations across the globe and is a problem that exists across all classes of pharmaceutical agents. More recently, legislation has been enacted to overcome this current state of affairs with varying success. This article will highlight the historical lack of paediatric specific data for pharmaceutical agents, discuss the evolving landscape of legislation aimed to reverse this problem, report on the impact of this legislation for antifungal therapies, and comment on the need for future advancement to improve efficiency for access to paediatric data.

History of Approval of Pharmaceutical Agents

The oldest consumer protection agency in the USA, the Food and Drug Administration (FDA), dates back to the enactment of the Pure Food and Drugs Act in 1906. The FDA's regulatory capacity increased dramatically with the passage of the 1938 Food, Drug, and Cosmetic Act. This act was in direct response to the unregulated distribution of a sulfanimide elixir by a pharmaceutical company for the treatment of infections in children. The elixir was produced by dissolving the sulfonamide powder in diethylene glycol. Children exposed to the diethylene glycol suffered from significant pain, renal insufficiency, and in many cases death [6].

The suffering sustained by the children exposed to the sulfanimide elixir directly enhanced the regulatory power of the FDA. Ironically, this increase in regulatory power resulted predominantly in better-informed adult indications for medications and not paediatric indications. Despite subsequent acts in 1979 and 1994 requiring paediatric information and allowing for paediatric drug labeling [7], respectively, the inadequacy of paediatric specific data persisted. A survey of the 1973 Physician's Desk Reference found that 78 % of the listed medications either lacked a paediatric indication or contained a disclaimer for paediatric use. A similar review of the 1991 Physician's Desk Reference found that 81 % of the medications contained a disclaimer for paediatric use [8].

More recently Shah et al. used a large multicenter administrative database to evaluate the off-label utilization of 90 different medications for hospitalized children. They found that close to 80 % of paediatric hospitalizations were inclusive of the administration of one of these medications in an off-label setting and that off-label medications accounted for 40 % of the expenditures for the 90 pharmaceutical agents [9]. In 2006, Yoon et al. reviewed all medications listed in the *Harriet Lane Handbook*, a common reference used to inform dosing regimens of medications for children, to determine if a listed medication had a specific paediatric label [10]. They found that overall, 27 % of medications listed in this paediatric specific reference were off-label indications. After grouping the listed medications into 19 classes of agents, they found that the percentage of off-label agents in each class ranged from 3 % to as high as 57 %. This was an improvement from the aforementioned data from the 1970s and early 1990s and may reflect some of the regulatory changes detailed below. Nonetheless, these rates are still too high.

Legislation to Improve Availability of Paediatric Specific Data

The challenges presented by the limited availability of paediatric specific data for pharmaceutical agents have been well recognized by regulatory agencies such as the FDA and the European Medicines Agency (EMA). In the past few decades, a number of legislative steps have been enacted in a "carrot" and "stick" approach to require industry to produce paediatric specific pharmacokinetic (PK) and pharmacodynamics (PD) data in exchange for extension of patents.

The recent evolution of paediatric specific pharmaceutical legislation is well documented in a recent review [11] and the chronology of this legislation is listed in Table 1. The modern movement to improve the availability of paediatric data dates back to 1997 with the Food and Drug Administration Modernization Act (FDAMA). FDAMA included a rule that offered a pharmaceutical company 6 months of additional patent protection on a medication if they provided results from an FDA-approved paediatric study for the drug prior to patent expiration. Under this legislation, the FDA could request but not require that a pharmaceutical company produce paediatric specific data for a drug. The 6-month patent exclusivity offer was continued in 2002 under the Best Pharmaceuticals for Children Act (BPCA). Unfortunately, like the preceding legislation, the BPCA only offered the "carrot" (6-month exclusivity to the pharmaceutical company) but did not have the "stick" (the FDA did not have the ability to require paediatric studies). The proposed and initially approved Paediatric Final Rule was an attempt to give the FDA the "stick" but the Paediatric Final Rule was eventually overturned by the Federal District Court. The "stick" would eventually come in 2003, in the form of the Paediatric Research Equity Act (PREA). The PREA granted the FDA the authority to require pharmaceutical companies to establish a plan for paediatric specific studies when a new drug application is submitted.

Ultimately the BPCA and the PREA were reauthorized in 2012 under a single act, the Food and Drug Administration Safety and Innovation Act (FDASIA). FDASIA permanently authorized the BPCA and PREA and formalized the process that would be required of pharmaceutical companies regarding paediatric drug studies. Typically at the completion of Phase II trials for a new drug, the pharmaceutical company and FDA will meet to discuss a Paediatric Study Plan (PSP).

Table 1 Recent US and European legislation to improve paediatric pharmaceutical data

Legislation	Implication
USA	
1997 Food and Drug Administration Modernization Act (FDAMA)	FDA offers pharmaceutical companies an additional 6-month exclusivity for a drug in exchange for paediatric specific data
2002 Best Pharmaceuticals for Children Act (BPCA)	Continuation of stipulations initially legislated under FDAMA
2003 Paediatric Research Equity Act (PREA)	FDA granted the authority to require pharmaceutical companies to establish a plan for paediatric specific studies when a new drug application is submitted
2012 Food and Drug Administration Safety and Innovation Act (FDASIA)	Permanently authorized the BPCA and PREA and formalized the process that would be required of pharmaceutical companies regarding paediatric drug studies
Europe	
2006 European Parliament and the Council of the European Union Paediatric Regulation No 1901/2006 (Paediatric Regulation)	EMA requires a paediatric investigation plan to be developed and performed for all newly developed drugs in exchange for an additional 6-month exclusivity

FDA food and drug administration, *EMA* European medicines agency

Within 60 days of this meeting, the company is required to submit a formal PSP which can be a request for a waiver to perform paediatric studies, a request for deferral, or an outline of proposed studies. Waivers are only granted if paediatric studies are deemed impossible or impracticable, if the product is thought to be unsafe in children, or if the product is unlikely to be used in paediatric patients. The FDA's internal Paediatric Review Committee (PeRC) then reviews the submitted PSP. The PeRC is expected to take 3 months to provide recommended changes to the PSP. Subsequently, a final PSP inclusive of PeRC recommendations is expected to be submitted by the pharmaceutical company within 3 months [12].

A parallel European movement to improve timely access to appropriate paediatric dosing began with an EMA round table discussion in 1997 that culminated in a 2002 report entitled *Better Medicines for Children* [13]. This report served as an outline for a regulation that was eventually enacted in 2006 referred to as The European Parliament and the Council of the European Union Paediatric Regulation No 1901/2006 (Paediatric Regulation). The goals of the Paediatric Regulation were to increase the availability of well-studied medicines to children and to make paediatric specific pharmaceutical data widely available. The Paediatric Regulation had a similar "carrot and stick" format as the FDA regulations. At the time a pharmaceutical company completes human PK studies in adults, they are required to submit a paediatric investigation plan (PIP). Analogous to the PSP, the PIP can be a request for a waiver to perform paediatric studies, a deferral for performing paediatric studies, or a proposal for what paediatric studies will be performed. Waivers are only granted if the pharmaceutical agent is predicted to be unsafe or ineffective in children or treats a disease that does not occur in children. The EMA's appointed Paediatric Expert Committee (Paed Co) then reviews the PIP and is expected to respond with requested modifications within 90 days. The pharmaceutical company incorporates the requests into the PIP and returns it to Paed Co, which then submits their final PIP recommendation to the EMA. Eventually, after the completion of the paediatric studies documented in the PIP, the pharmaceutical company will receive a 6-month extension on their medication's patent. For medications that are already off-patent, a company can apply for a Paediatric Use Marketing Authorisation, which would provide 10 years of marketing protection. The latter is voluntary while a PIP is required for all new drugs [14, 15].

Impact of Recent Legislation

The legislation discussed above has significantly empowered both the FDA and EMA in similar ways to require pharmaceutical companies to devise plans for establishing relevant paediatric data for newly developed drugs. The effectiveness of this legislation has been evaluated in recent years in both the USA and Europe. Wharton et al. retrospectively reviewed all FDA-written requests issued to pharmaceutical companies between 1998 and 2012 and determined whether paediatric specific studies were performed in exchange for this extended exclusivity [16]. In response to 401 FDA-written requests, pharmaceutical companies performed paediatric studies for 189 (47 %) of these requests all resulting in a subsequent 6-month patent extension of the drug studied. The paediatric data resulted in a paediatric specific labeling change for 173 (92 %) of these agents. While these results

are encouraging, not all of the paediatric label changes were for a new paediatric indication. In fact, paediatric efficacy trials found 78 of these agents to be ineffective in children, and thus, a new paediatric indication was not found.

It appears that the European legislation has also had a positive impact on the number of paediatric clinical trials being initiated [17]. Wimmer et al. found that within 7 years of the Paediatric Regulation, there have been 511 unique PIPs that the EMA's PaedCo authorized [15]. Of the 511 PIPs, 46 were for new drugs and 17 were for off-patent drugs that the EMA had previously identified as needing paediatric data. As of the time of that publication, 17 of the PIPs were completed and passed the PaedCo compliance review. It is not clear how many of these resulted in a paediatric label change.

Paediatric Approval of Antifungal Agents

Since the turn of the century, six antifungal agents have received approval for use in adults both from the FDA and the EMA (Table 2). The aforementioned legislation to promote paediatric pharmaceutical research has promoted the development, initiation, and completion of a number of paediatric-specific studies for many of these antifungal agents. There are now FDA- and EMA-approved paediatric indications for both caspofungin and micafungin, and the EMA has granted a paediatric indication for voriconazole down to 2 years of age. Additionally, there are active paediatric posaconazole PK studies and the EMA has approved a PIP that outlines isavuconazole studies to be performed in children in the near future.

Limitations of the Legislation

Certainly, the era of paediatric specific pharmaceutical legislation has translated into improved paediatric data for many drugs including antifungal agents. However, it needs to be noted that there still remains a significant delay in the time from the initial adult approval of a medication to the first paediatric-approved indication. For example, caspofungin has an FDA- and EMA-approved paediatric indication but these paediatric indications did not come until 7 years after the initial adult approval. Voriconazole still does not have an FDA-approved paediatric indication and posaconazole has neither an FDA- or-EMA approved indication. Isavuconazole has only recently received an adult indication and it will likely be years before a paediatric approved dose is available.

The significant delay between adult- and paediatric-approved indications creates an environment for off-label use with potential negative consequences. Because of the traditional lack of paediatric-specific pharmaceutical data, paediatricians have become accustomed to prescribing off-label medications to their patients. The perceived need to administer antifungal agents in an off-label scenario may be greater than with other pharmaceutical agents for multiple reasons: the number of currently available antifungal agents is limited, some of them have undesirable side effects, and only a few have an enteral option. However, in the absence of paediatric-specific PK and PD data, decisions on paediatric dosing regimens are extrapolated from available adult data, which can lead to negative outcomes. The experience with voriconazole is a cautionary tale as to why this approach can prove dangerous especially when treating life-threatening IFD.

After initial approval of voriconazole in 2002, many clinicians began administering voriconazole to children in the absence of paediatric-specific dosing recommendations.

Table 2 Adult and paediatric approved antifungal agents since 2000

Recently approved antifungal agents	FDA approval dates		EMA approval dates	
	Adult	Paediatric	Adult	Paediatric
Voriconazole	2002 (Oral/IV) 2003 (Oral suspension)	2002 (12 years and older only)	2002 (oral/IV) 2004 (oral suspension)	Approved down to 2 years of age[a]
Posaconazole	2006 (Oral suspension) 2013 (DR tablets) 2014 (IV)	2006 (13 years and older only)	2005 (Oral suspension) 2014 (DR tablets) 2015 (IV)	None
Isavuconazole	2015 (IV/Oral)	None	2015 (IV/Oral)	None
Anidulafungin	2006	2006 (16 years and older)	2007	None
Caspofungin	2001	2008	2001	2008
Micafungin	2005	2013	2008	2008

Data identified from the following websites all accessed on December 10, 2015: http://www.fda.gov/Drugs/default.htm, http://dailymed.nlm.nih.gov, and http://www.ema.europa.eu/

DR delayed release, *IV* intravenous, *FDA* food and drug administration, *EMA* European medicines agency

[a] Not apparent when approval granted or what dosing is supported

Ultimately, in 2009, Neely et al. reported the voriconazole trough concentrations from 46 children receiving a wide variety of enteral and parenteral dosing regimens [18]. Of the 46 children, most had proven probable or possible invasive fungal infection. Patients who had a voriconazole trough below 1000 ng/mL had a significantly increased risk of death compared to children with trough levels above 1000 ng/ml (RR 6.3, 95 % CI 1.6–24.0). In a simulation model leveraging the data from these children, they found that even with a dose of 7 mg/kg every 12 h, only two thirds of children would achieve a target trough level above 1000 ng/ml. More recent publications evaluating a range of voriconazole doses suggest an intravenous loading dose of 9/mg/kg every 12 h for two doses followed by 8 mg/kg/dose every 12 h for children ages 2 through less than 12 years [19, 20]. These doses are much higher than adult doses and would suggest that voriconazole administration in children was previously grossly underdosed likely leading to failures. Notably, it is not apparent that the FDA or EMA has approved the higher dosing regimens. This scenario highlights the potential dangers of using antifungal agents in children with IFD in an off-label setting.

The gap between an approved adult indication and an approved paediatric indication is a direct result of the ethical concern for initiating paediatric studies prior to availability of adult data coupled with inherent delays related to the current legislative design. First, the iterative process that is required to produce the FDA-directed PSP and the EMA-directed PIP can in and of itself take months or longer to reach an agreed upon plan for paediatric studies. The studies will then take years to complete after which the data need to be reviewed and approved by the FDA and/or EMA. Unless the initial studies are performed in children, this process guarantees that there will be multiple years between an adult approved indication and a paediatric-approved indication. If the pharmaceutical company initially submits for a deferral to perform paediatric studies, the process may be delayed for an additional 3–5 years [17]. Therefore, under this current system, the long time period in which a medication will be available to paediatric clinicians for off-label use will continue to exist.

Future Directions for Improvement

Successfully reducing the time period between adult and paediatric approvals would likely require that paediatric studies be performed in parallel to or prior to adult studies. As noted above, paediatric studies are often delayed under the ethical concern that safety must first be established in adults prior to exposing children to a medication. In the past, a distinction has been made between the safety of administering an unapproved medication to children in a clinical setting and the safety of administering that same medication in a research setting. The contention is that a physician prescribing an unapproved medication in a clinical setting can do so more safely by "consulting with appropriate physicians experienced in the use of such a drug" [21]. It can be argued that administration of a medication in an unapproved setting without the structure of a research protocol can be equally unsafe and unethical, and therefore, this distinction should be reconsidered.

Beyond considering paediatric studies early in the investigational process, there also needs to be better paediatric infrastructure for conducting paediatric studies. Such infrastructure would be inclusive of research teams across multiple institutions skilled at enrolling paediatric patients and performing drug studies. This would greatly improve the efficiency of paediatric studies once they are started. The Paediatric Trials Network (paediatrictrials.org) funded by the National Institute of Child Health and Human Development is an example of such a research group. Similar groups specifically focused on antifungal agents are needed.

Conclusion

Since the turn of the century, a number of new antifungal agents have received EMA and FDA approval greatly enhancing the options for the treatment of IFD. Backed by recent legislation, the FDA and EMA have also committed to improving the availability of paediatric data for newly released medications. These actions have resulted in paediatric indications for a number of the new antifungal agents. However, there is a lack of efficiency in the current process that results in significant delays in approved paediatric indications relative to adult indications. The next steps need to focus on reducing this gap with an ultimate goal of concurrent approvals for both paediatric and adult patients.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. O'Shea JJ, Kanno Y, Chan AC. In search of magic bullets: the golden age of immunotherapeutics. Cell. 2014;157:227–40.
2. Wingard JR, Majhail NS, Brazauskas R, et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol. 2011;29:2230–9.

3. Kamran Hejazi Kenari S, Mirzakhani H, Saidi RF. Paediatric transplantation and tolerance: past, present, and future. Paediatr Transplant. 2014;18:435–45.
4. Majhail NS, Rizzo JD. Surviving the cure: long term followup of hematopoietic cell transplant recipients. Bone Marrow Transplant. 2013;48:1145–51.
5. Gubbins PO, Anaissie EJ. Antifungal therapy. In: Anaissie EJ, McGinnis MR, Pfaller MA, editors. Clinical mycology. China: Elsevier Health Sciences; 2009.
6. Wax PM. Elixirs, diluents, and the passage of the 1938 federal food, drug and cosmetic act. Ann Intern Med. 1995;122:456–61.
7. Novak E, Allen PJ. Prescribing medications in paediatrics: concerns regarding FDA approval and pharmacokinetics. Pediatr Nurs. 2007;33:64–70.
8. Guidelines for the ethical conduct of studies to evaluate drugs in paediatric populations. Committee on Drugs, American Academy of Paediatrics. Paediatrics. 1995; 95:286–294.
9. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. Arch Pediatr Adolesc Med. 2007;161:282–90.
10. Yoon EY, Davis MM, El-Essawi H, Cabana MD. FDA labeling status of paediatric medications. Clin Paediatr. 2006;45:75–7.
11. Rivera DR, Hartzema AG. Paediatric exclusivity: evolving legislation and novel complexities within paediatric therapeutic development. Ann Pharmacother. 2014;48:369–79.
12. Food and Drug Administration. Retrospective review of information submitted and actions taken in response to PREA 2003. Available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM197636.pdf. Accessed 10 Dec 2015.
13. European Commission. Better medicines for children. 2002. Available at: http://ec.europa.eu/health/files/pharmacos/docs/doc2002/feb/cd_paediatrics_en.pdf. Accessed 10 Dec 2015.
14. Saint Raymond A, Seigneuret N. The European paediatric initiative: 1 year of experience. Paediatr Drugs. 2009;11:9–10.
15. Wimmer S, Rascher W, McCarthy S, Neubert A. The EU paediatric regulation: still a large discrepancy between therapeutic needs and approved paediatric investigation plans. Paediatr Drugs. 2014;16:397–406.
16. Wharton GT, Murphy MD, Avant D, et al. Impact of paediatric exclusivity on drug labeling and demonstrations of efficacy. Paediatrics. 2014;134:e512–8.
17. Olski TM, Lampus SF, Gherarducci G, Saint RA. Three years of paediatric regulation in the European Union. Eur J Clin Pharmacol. 2011;67:245–52.
18. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J. Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis. 2010;50:27–36.
19. Mori M, Kobayashi R, Kato K, et al. Pharmacokinetics and safety of voriconazole intravenous-to-oral switch regimens in immunocompromised Japanese paediatric patients. Antimicrob Agents Chemother. 2015;59:1004–13.
20. Friberg LE, Ravva P, Karlsson MO, Liu P. Integrated population pharmacokinetic analysis of voriconazole in children, adolescents, and adults. Antimicrob Agents Chemother. 2012;56:3032–42.
21. Unapproved uses of approved drugs: the physician, the package insert, and the Food and Drug Administration: subject review. American Academy of Paediatrics Committee on Drugs. Paediatrics 1996; 98:143–145.