Food and Drug Administration

Meeting of the Advisory Committee for Pharmaceutical Science

and

Clinical Pharmacology

March 2nd , 2011

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Food and Drug Administration
Center for Drug Evaluation and Research
Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)
March 2, 2011
Dallas, TX

DRAFT AGENDA

7:15	Call to Order	Jurgen Venitz, M.D., Ph.D. Acting Chair, ACPS-CP
	Conflict of Interest Statement	Yvette Waples, Pharm.D. Acting Designated Federal Official, ACPS-CP
0730	Introduction and Background	Lawrence Lesko, Ph.D. Director, Office of Clinical Pharmacology (OCP) OTS, CDER, FDA
0800	FDA perspective on rare disease drug development and regulation	Tim Cote, M.D., MPH Director, Office of Orphan Products Development, FDA
0830	Importance of mechanistic understanding of disease and response biomarkers	Trevor Mundel, M.D. (Guest Speaker) Global Head of Development, Novartis Pharma AG
0900	A clinical pharmacology decision tree for orphan drugs	Dennis Bashaw, Pharm.D. Director, Division of Clinical Pharmacology 3 OCP, OTS, CDER, FDA
0930	Clinical pharmacology tools for developing drugs for rare diseases	Christine Garnett, Pharm.D. Associate Director Operations, Pharmacometrics OCP, OTS, CDER, FDA
1000	BREAK	
1020	Future perspectives on academic-industry-government collaboration on orphan drug development	James Cloyd, Pharm.D. Professor, Director of Ctr. For Orphan Drug Development, University of Minnesota
1040	Clarifying Questions	
1100	Open Public Hearing	
1200	Lunch	
1300	Committee Questions and Discussions	Jurgen Venitz, M.D., Ph.D. Acting Chair, ACPS-CP
1420	FDA next steps	Anne Pariser, M.D. Associate Director for Rare Diseases Office of New Drugs (OND), CDER, FDA
1435	FDA Closing Remarks	Lawrence Lesko, Ph.D. Director, OCP, OTS, CDER, FDA

Questions for the Clinical Pharmacology Advisory Committee
March 2, 2011

Topic 1: Mechanistic Understanding of Disease and Response Biomarkers

1-1. How can prior preclinical and early clinical information on rare/orphan disease biology and an understanding of drug pharmacology be ideally leveraged to inform the design and analysis of clinical pharmacology studies and phase 2/3 clinical trials?

Topic 2: Clinical Pharmacology Decision Tree for Rare/Orphan Drugs

2-1. ***[Voting Question].*** Are the drug development paradigms for pediatric and oncologic drug development well suited as processes for **re-purposing** of approved drugs for new rare/orphan drug indications?

If yes, what types of prior information or modifications would strengthen the paradigms?

If no, what additional scientific and regulatory considerations should be addressed?

2-2. For **new molecular entities** intended for drugs for rare/orphan diseases, does the committee have recommendations on the primary (required) and secondary (optional) clinical pharmacology data that are needed for safe and effective use of the drugs?

2-3. ***[Voting Question].*** Do the current drug development programs and clinical pharmacology studies for rare/orphan diseases provide sufficient information on drug safety given the relatively small size of the pivotal efficacy trials?

If yes, what can be done to strengthen further the safety information derived from the development programs?

If no, what additional safety issues may not have been addressed and what is the best way to address them?

Topic 3: Clinical Pharmacology Tools for Developing Drugs for Rare Diseases

3-1. ***[Voting Question].*** Does the committee agree with, and endorse, a quantitative model-based (pharmacometrics) approach to drug development and regulatory decision-making (e.g., trial design, dose selection and support for labeling and approvals) for rare/orphan diseases?

3-2. Are there other innovative tools and approaches that FDA should consider to enable drug development such as novel study designs, genetics or new clinical endpoints (biomarkers)?

Topic 4: FDA Next Steps

4-1. Does the committee have recommendations for the future direction that FDA is taking in clinical pharmacology or other areas of rare/orphan disease drug development, including collaboration with academia and other government agencies?

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13. Cardiovascular and Renal Drugs Advisory Committee Meeting: Revatio (sildenafil) for the treatment of pediatric pulmonary arterial hypertension (PAH) (July 29, 2010) (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm192863.htm)

* A copy of the paper is included in the attachments.

Attachment 1.

Institution of Medicine Brief: Rare Diseases and Orphan Products--Accelerating Research and Development (October 2010)
www.iom.edu/rarediseaseresearch

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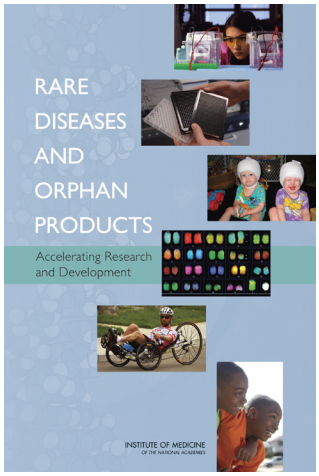
For more information visit www.iom.edu/rarediseaseresearch

Rare Diseases and Orphan Products

Accelerating Research and Development



Rare diseases collectively affect millions of Americans of all ages and additional millions of people globally. Of the estimated 5,000 to 8,000 diseases categorized as rare, some affect only a few individuals, while others affect many thousands of people. Most of the diseases are genetic or have a genetic component. Others arise from such factors as exposure to infections or toxins. Rare diseases often are serious and life-altering; many are life-threatening or fatal.

Because each rare disease affects a relatively small population, developing drugs and medical devices to prevent, diagnose, and treat these conditions is challenging. These difficulties include attracting public and commercial funding for research and development, recruiting sufficient numbers of research participants, designing sound clinical trial strategies for small populations, and assessing the safety and efficacy of products before they are marketed. Scientists, medical products companies, government policy makers, and private advocacy groups have done much in recent decades to respond to these challenges; advances in prevention, diagnosis, and treatment have brought significant benefits for many patients and their families.

Because each rare disease affects a relatively small population, developing drugs and medical devices to prevent, diagnose, and treat these conditions is challenging.

Nonetheless, researchers still lack even a basic understanding of the cause or underlying molecular mechanisms of many rare diseases. Also, effective therapeutics are available for only a small fraction of rare diseases—and even when available, some therapies are extraordinarily expensive. To help in accelerating rare diseases research and product development, the National Institutes of Health (NIH), with support from the Food and Drug Administration (FDA), asked the Institute of Medicine (IOM) to examine the opportunities and obstacles in developing drugs and medical devices for treating rare

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diseases—sometimes called "orphan" diseases because their limited prevalence often has discouraged both private and public research.

Toward an Integrated National Strategy

As an overarching goal, the report, *Rare Diseases and Orphan Products: Accelerating Research and Development*, calls for implementing an integrated national strategy to promote rare diseases research and product development. The strategy would include seven key elements:

1. Active involvement and collaboration by a wide range of public and private interests, including government agencies, commercial companies, academic institutions and investigators, and advocacy groups.
2. Timely application of advances in science and technology that can make rare diseases research and product development faster, easier, and less expensive.
3. Appropriate use and further development of trial design and analytic methods tailored to the special challenges of conducting research on small populations.
4. Creative strategies for sharing research resources and infrastructure to make good and efficient use of scarce funding, expertise, data, biological specimens, and participation in research by people with rare conditions.
5. Reasonable rewards and incentives for private-sector innovation and prudent use of public resources for product development when the latter appears to be a faster or less costly way to respond to important unmet needs.
6. Adequate organization and resources, including staff with expertise on rare diseases research and product development, for the public agencies that fund biomedical research on rare diseases and regulate drugs and medical devices.
7. Mechanisms for weighing priorities for rare diseases research and product development, establishing collaborative as well as organization-specific goals, and assessing progress toward these goals.

Components of each of these elements already exist, some more robust than others. However, it is difficult to achieve coherence, given the array of participants with differing perspectives and priorities, the number and diversity of rare diseases, and the limited and even undocumented resources devoted to them individually and collectively. Thus, the IOM report recommends a number of steps to aid in developing a more integrated approach to rare diseases research and product development.

As one opportunity for improvement, NIH should develop a comprehensive action plan for rare diseases research that covers all institutes and centers and that defines and integrates goals and strategies. This plan should cover program planning, grant review, training, and coordination of all phases of research. Other recommendations span a range of areas, from improving how drugs and medical devices developed for rare diseases are covered under the government's regulatory umbrella to gaining a better understanding of how public and private insurance programs influence the development and use of such drugs and medical devices.

Accelerating Discovery Research

Basic research, followed by discovery research, is key in identifying the causes and molecular mechanisms of rare diseases and in pinpointing therapeutic targets. In recent years, the research tools available to biomedical investigators have improved dramatically, and some of them hold particular promise for rare diseases research. Also promising is the growth of public-private partnerships and other collaborations that are deploying

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new strategies to bridge the gulf between basic research findings and beneficial products.

Given the small number of patients available to participate in research on rare diseases, as well as limited funding, it is particularly important to make best use of the resources for research and the data and other resources generated by research. The report therefore recommends that NIH work with industry, academia, and voluntary organizations to develop a comprehensive system of shared resources for discovery research on rare diseases and to facilitate communication and cooperation for such research. This effort should include, among other actions, the creation of a repository of publicly available animal models for rare disorders that reflect the disease mechanisms seen in humans and a public repository of biological data on the molecular mechanisms of rare diseases generated by investigators funded by NIH, private foundations, and industry.

Supporting Clinical Research

Once a potential drug has been discovered, the process of developing it into a marketable product begins with preclinical trials and continues through increasingly demanding phases of clinical testing. This process is expensive and risky. The federal government, through the Orphan Drug Act of 1983, provides commercial firms with various incentives for undertaking clinical trials. NIH also supports such efforts through its Rare Diseases Clinical Research Network and other programs. The IOM report recommends that more be done to identify and implement collaborative strategies to share and leverage resources with a view to decreasing research and development costs without sacrificing product safety or efficacy.

To this end, NIH should increase its capacity and flexibility to support all phases of preclinical and clinical research related to rare diseases, including clinical trials of new and repurposed therapeutic agents. Several opportunities should be explored, including the provision of preclinical development services to nonprofit entities and the creation of standards for data and specimen collection, maintenance, and sharing for patient registries and biorepositories. NIH should also coordinate the new Cures Acceleration Network with the Rare Diseases Clinical Research Network, the Clinical and Translational Science Awards program, the grants programs of FDA's Office of Orphan Product Development, and other existing initiatives.

Establishing a Task Force

To help build on these and other recommendations and existing activities, the IOM report calls for the Secretary of the Department of Health and Human Services to establish a national task force on accelerating rare diseases research and product development. To operate for perhaps four to eight years, the task force would bring together leaders from government, industry, academic and other research institutions, and advocacy groups. Its objectives would be to promote, coordinate,

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monitor, and assess the implementation of NIH, FDA, and other public- and private-sector initiatives on rare diseases and orphan products and to support additional opportunities for public-private collaboration.

Conclusion

Even as the task force acts to foster cooperation and collaboration, all participants in rare diseases research and product development will need to improve their individual efforts. Individual improvement will strengthen the foundation for collaboration.

Overall, the effort and investment needed to move further toward a collaborative, coordinated, open, and sustained approach to rare diseases will be substantial, but not making the investment will also be costly. The potential benefits justify a renewed commitment to accelerating rare diseases research and orphan product development.

Committee on Accelerating Rare Diseases Research and Orphan Product Development

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Attachment 2.

HE Heemstra, S van Weely, HA Buller, H GM Leufkens and R LA de Vrueh.
Translation of rare disease research into orphan drug development: disease matters.
Drug Discovery Today. 14: 1167-1173, 2009.

Translation of rare disease research into orphan drug development: disease matters

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More than 25 years of orphan drug regulations have yielded several new treatments for patients with rare diseases. Here, we show that successful translation of rare disease research into an orphan drug discovery and development programme is dependent on the disease class, its prevalence and the disease-specific scientific output. Our findings indicate that current orphan drug legislation alone is not sufficient to stimulate orphan drug development for diseases with a very low prevalence. Consequently, additional incentives should focus on stimulating the specific needs of rare disease research at disease class level.

Introduction

It has been estimated that between 5000 and 8000 rare diseases exist, many of which are of genetic origin, affect children at a very early age and are life threatening and/or chronically debilitating [1,2]. Rare diseases exist in all disease classes and range from exceptionally rare diseases that occur in only a few individuals worldwide to more prevalent, but still considered rare, disorders such as cystic fibrosis and narcolepsy – cataplexy. Criteria for a rare disease differ slightly by region. In the USA, a rare disease is defined as a disease that affects less than 200,000 inhabitants, equivalent to approximately 6.5 patients per 10,000 inhabitants [3]. In the European Union (EU), however, a rare disease needs to be life threatening or chronically debilitating, besides having a prevalence of less than 5 patients per 10,000 inhabitants [3]. In the past 25 years, it has been recognized by various authorities that because of the rarity of these diseases, the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat a rare condition would not be recovered by the expected sales of the medicinal product under normal market conditions [4–6]. Therefore, specific legislation to stimulate the discovery and development of drugs for rare diseases – the so-called 'orphan drugs' – has been introduced: in the USA in 1983 [4], in Japan in 1993 [5] and in the EU in 2000 [6]. Sponsors of a potential product for a rare disease can apply at the US Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) for an orphan designation, which results in various benefits that aid the full development of their products. These incentives include reduction of regulatory fees, extra regulatory guidance and a marketing exclusivity period of seven years (USA) or ten years (EU) after approval of the product [3,4,6]. As of March 2009, in the USA, nearly 2000 orphan designations have been assigned, and more than 300 products have been approved for marketing [7]. The EU has approved more than 50 orphan medicinal products and assigned more than 600 orphan designations [8,9]. It is widely acknowledged that these numbers demonstrate how both regulations have been successful in stimulating orphan drug discovery and development by the pharmaceutical industry, particularly in small- and medium-sized enterprises (SMEs), resulting in an important improvement in the situation of specific groups of patients in the USA and the EU [5,7,10,11].

Although these regulations have been instrumental, they are not the only driving force behind the discovery and development of therapies for patients suffering from rare disorders. In two earlier studies, we focussed on success factors in orphan drug discovery and development. First, we showed that the experience of a company in developing orphan drugs is an important predictor for the authorization of orphan drugs [12]. Second, we revealed a strong relationship between orphan drug development and pharmaceutical

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innovation performance (composed of level of R&D expenditure, number of pharmaceutical patents and number of SMEs) in Europe [13]. Here, we specifically focus on the translation of rare disease research into orphan drug development. Only fundamental and clinical research into a rare disorder (such as aetiology, diagnosis and genetics [14]) can reveal the necessary drug targets, which, in turn, can be translated into the discovery of potentially interesting drug leads and subsequent drug development [15]. Development of an orphan drug is thus the actual translation of the findings from fundamental and clinical rare disease research, much of it publicly funded. In both the USA and the EU, certain disease classes – in particular oncology – are associated with a high number of orphan designations and approvals, compared with disease classes with less orphan designations [5,10,11]. This skewed distribution of orphan drug development over the disease classes indicates that certain disease-specific factors exist that favour the translation of rare disease research into orphan drug development. Apart from disease class, we focussed on rare disease research output because the understanding of a (rare) disease forms the necessary foundation for any successful (orphan) drug discovery and development programme. Disease prevalence, an important reason for the implementation of the current orphan drug legislation, was included as a third disease-specific factor.

The aim of this study was to analyze the influence of these three major disease-specific factors on the chance for a rare disease to obtain at least one product with an orphan designation. Considering the low number of rare diseases for which a therapy is being developed, increased knowledge of the underlying translational process will provide better input for novel approaches to improve orphan drug development. Whereas a lack of sponsor interest will call for additional (economic) incentives, a hampered translation of rare disease research findings into orphan drug development might require novel incentives that lie beyond the scope of current incentives that aim to enhance orphan drug discovery and development.

Rare diseases

Publications on rare diseases

This study included all rare diseases that have been reported in the Orphanet report series on prevalence of rare diseases (May 2008 issue), a systematic survey of the literature that is being performed to provide an estimate of the prevalence of rare diseases in Europe [16]. The report series contains prevalence figures of more than 1500 rare diseases, making it the largest publicly available dataset with rare disease prevalence figures currently available. The dataset was extended with 102 rare diseases for which an orphan

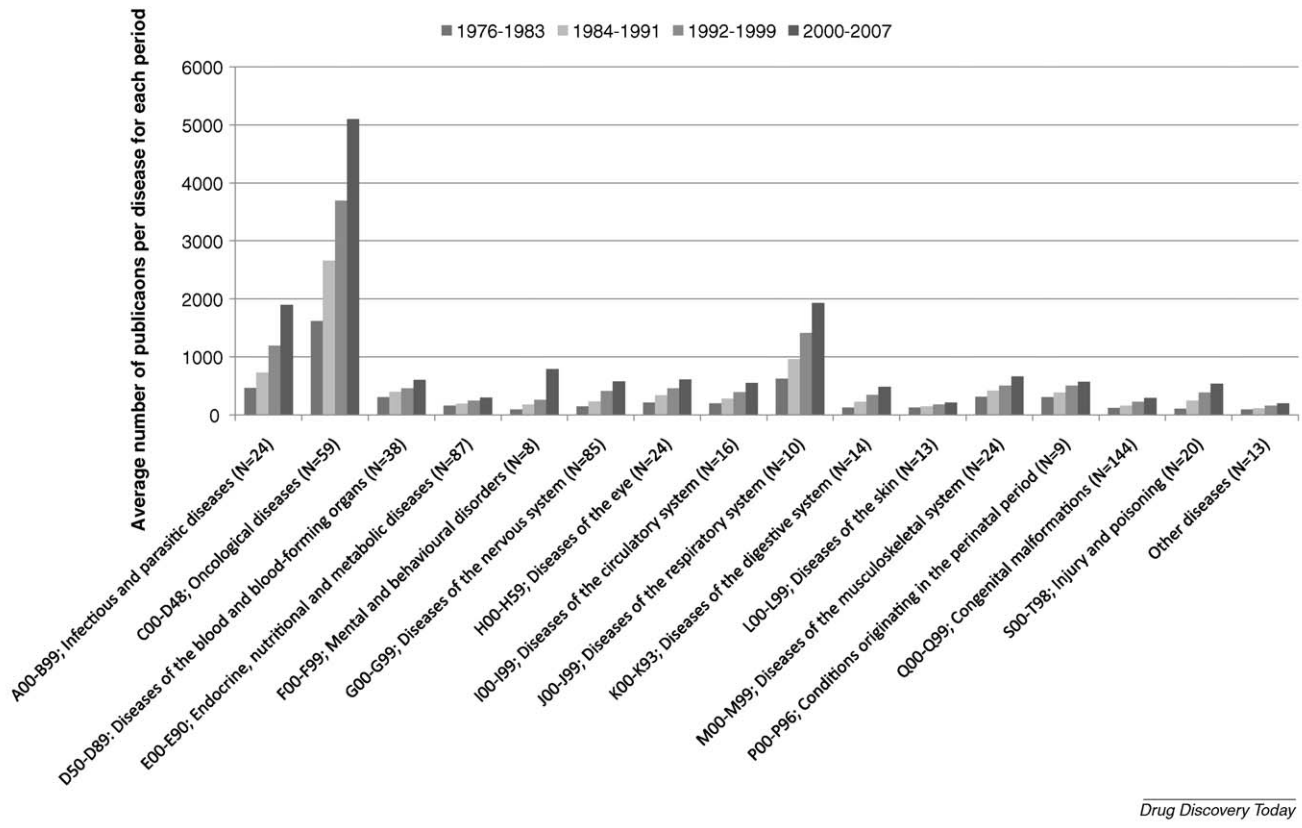

FIGURE 1

Average number of publications per disease, by disease class and time period. The number of publications of each rare disease included in the study was determined with a search in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/). For each disease, a PubMed search string was composed consisting of the disease name and synonyms of the disease mentioned in the Orphanet database (http://www.orpha.net). Possibilities for wrongful inclusion of a publication caused by a disease with the name of an author (e.g. Wilson disease) or a geographic region (e.g. Japanese encephalitis, West syndrome) were addressed by including Boolean NOT statements and PubMed search field tags for these terms, in a way comparable to that of Mendis and Mclean [53]. All searches were limited to English language articles and original research or case reports only. Reviews, comments and letters were excluded.

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designation was assigned but that were not mentioned in the Orphanet report series. Exceptionally rare diseases with a prevalence below 0.1/100,000 were excluded from the study because orphan drug development in this group was found to be nearly absent (see http://www.emea.europa.eu/htms/human/orphans/opinions.htm; accessed March 2009). Finally, diseases included in the study were classified according to disease class, based on the International Classification of Diseases (ICD), edition 10 (http://www.who.int/classifications/apps/icd/icd10online/; accessed February 2009).

The disease dataset consequently consisted of 588 rare diseases, distributed over 3 prevalence classes, with 161 diseases in the 0.1–0.9 per 100,000 prevalence group, 248 in the 1–9 per 100,000 group and 179 in the 10–50 per 100,000 group. More than 60% ($N = 375$) of the diseases included in the study belong to the disease classes (ICD; N) of oncological (C00–D48; 59); endocrine, nutritional and metabolic (E00–E90; 87); nervous system (G00–G99; 85); or congenital (Q00–Q99; 144) diseases. For each disease, we have determined the number of publications in four time periods: 1976–1983, 1984–1991, 1992–1999 and 2000–2007. Fig. 1 provides an overview of the average number of publications per disease for the disease classes that comprise at least 1% of the total number of diseases, for the consecutive time periods. The average number of publications per disease increased over time for all 588 diseases in the study, from 330 publications in the period 1976–1983 to 1319 publications in the period 2000–2007, indicating a consistent increase in scientific output from 1976 to 2007. The highest average number of publications per disease by far was found for the disease class of oncological diseases. At first glance, this increase in rare disease research is encouraging. However, comparison with the general increase of number of publications on overall biomedical research from 1976 to 2007 reveals that the observed increase is not statistically different from the general trend (data not shown). Moreover, the findings are inconclusive regarding whether implementation of specific orphan drug legislation in 1983 (USA) and 2000 (EU) has stimulated rare disease research worldwide.

Orphan drug discovery and development

A sponsor of a potential orphan drug has to submit to the regulatory authorities scientific evidence that confirms the rationale for the use of its medicinal product in the proposed orphan indication [6,7]. Consequently, an orphan designation can be regarded as a proxy indicator for the successful translation of rare disease research into an orphan drug discovery and development programme. In addition, an orphan designation indicates the interest of a sponsor in initiating an orphan drug development programme. For each rare disease included in the study, the number of orphan designations and the distribution of the designations over three time periods (1983–1991, 1992–1999 and 2000–2007) were determined by crosschecking these diseases against the FDA list of orphan designations and approvals (http://www.fda.gov/orphan/designat/list.htm; accessed February 2009) and the European Register of designated orphan medicinal products (http://www.ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm; accessed February 2009).

Disease-specific factors associated with orphan drug development

To verify the role of disease-specific factors in the translation of rare disease research into an orphan drug discovery and development programme, the association between rare disease prevalence, class and scientific output and the likelihood of a rare disease obtaining at least one product with an orphan designation in the

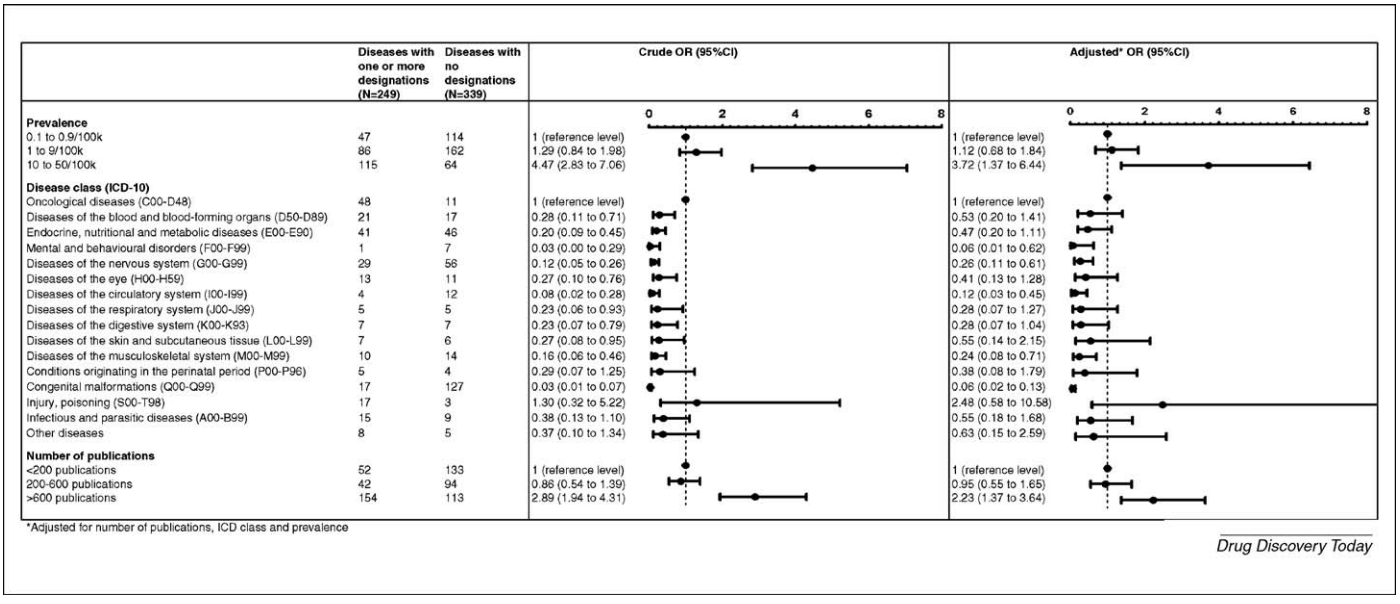

FIGURE 2

Characteristics of rare diseases ($N = 588$) potentially associated with obtaining at least one orphan designation in the US (1983–2007) or the EU (2000–2007). Characteristics of orphan drugs with and without at least one orphan designation were compared with univariate logistic regression analysis using SPSS Version 16 for Mac (SPSS, Chicago, IL). Odd ratios (ORs) and 95% confidence intervals (95%CI) were calculated for each of the categories in the three characteristics. The outcome was defined as obtaining at least one orphan designation in the US (1983–2007) or the EU (2000–2007). To test whether any of the characteristics were mutually related, a multivariate model was used in which the characteristics with statistically significant crude ORs were compared using a backwards stepwise selection method in which the removal testing was based on the probability of the likelihood-ratio statistic based on the maximum partial likelihood estimates.

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USA or the EU was determined. Odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated for each of these disease-specific characteristics in a logistic regression model (Fig. 2).

Prevalence

It was found that a disease with a prevalence between 10 and 50 per 100,000 had a more than threefold higher chance of obtaining at least one product with a designation (adjusted OR = 3.72; 95%CI = 1.37–6.44) than a disease with a prevalence of 0.1–0.9 per 100,000 (Fig. 2). The likelihood for a disease with a prevalence between 1 and 9 per 100,000 did not differ from that of a disease with a prevalence between 0.1 and 0.9 per 100,000. As mentioned in the Orphanet report series on the prevalence of rare diseases [16], it is difficult to assess the exact prevalence rate of each rare disease from the available data sources. It is likely that there is an overestimation for most rare diseases because the few published prevalence surveys are usually done in regions of higher prevalence and are usually based on hospital data. Therefore, the estimates included in the Orphanet report series are an indication of the assumed prevalence but might not be accurate [16]. We believe that the impact of the estimated prevalence rates on our findings is limited because our analyses were done at disease class or prevalence group level and not at the individual disease level. We conclude from the results that the likelihood for the initiation of an orphan drug development programme is associated with the prevalence of a rare disease, although these findings might be partly influenced by the association between scientific output and the prevalence of a rare disease. An explanation for the observed association between prevalence and the likelihood that an orphan drug is taken in development is a lack of commercial interest by potential sponsors. According to various sources, drug development is risky and costly [17–19]. Moreover, conducting a clinical trial for a rare disease results in many practical limitations, such as finding sufficient patients and statistical challenges [20]. These factors, combined with an intrinsic small market, make a favourable decision to develop a drug for less prevalent rare diseases unlikely [21,22], despite the incentives provided by current orphan drug legislation [3,23,24].

Disease class

Fig. 2 shows that oncological diseases were associated with the highest chance to obtain at least one product with an orphan designation, in particular when compared to mental and behavioural disorders (adjusted OR = 0.06; 95%CI = 0.01–0.62), diseases of the nervous system (adjusted OR = 0.26; 95%CI = 0.11–0.61), diseases of the circulatory system (adjusted OR = 0.12; 95%CI = 0.03–0.45), diseases of the musculoskeletal system (adjusted OR = 0.24; 95%CI = 0.08–0.71) and congenital malformations (adjusted OR = 0.06; 95%CI = 0.02–0.13). Congenital malformations were associated with a significantly lower chance to obtain at least one product with an orphan designation in comparison with all other disease classes (data not shown).

These findings are in line with findings by US and EU regulatory authorities that oncological diseases – and, to a lesser extent, endocrine, nutritional and metabolic diseases – comprise the highest number of orphan designations and approvals [7,10,11]. Clearly, the translation of rare disease research into orphan drug development requires certain characteristics that oncological diseases and endocrine, nutritional and metabolic diseases possess and congenital malformations lack. Successful translation of disease research into drug development consists of sufficient understanding of disease to discover the necessary drug targets and drug leads, which in turn can generate sufficient interest from sponsors to initiate a drug development programme [13,15,25–28]. Within oncology, an important boost was given to the translation of research by the 1971 National Cancer Act. This act provided the National Cancer Institute with not only the necessary funding and the mandate to support basic research but also the application of the results of the research to reduce cancer incidence, morbidity and mortality [29]. Since then, considerable public and private expenditures on oncology research, both in the USA and the EU, and a high-level transnational research infrastructure have evolved [30,31]. Consequently, knowledge and understanding of oncology have advanced rapidly and have turned oncology into an attractive niche indication for the pharmaceutical sector [32,33].

The observed differences between disease classes might also be explained by differences in the feasibility of identifying a suitable target and drug lead [27]. Within oncology, increased emphasis is given to targeted drug discovery [34]. A notable success in this area has been the development of imatinib, the first tyrosine kinase antagonist, which was introduced as an orphan drug for the treatment of chronic myelogenous leukaemia [35]. Most of these inhibitors were not approved for general cancer disease because of their broad action spectrum and non-specific actions (high evolutionary conservation of different kinases). However, when tested on rare cancer diseases, several of these kinase antagonists, originally developed for general cancer diseases, showed beneficial effects and were approved despite their non-specificity [36,37]. Similar important advances in the areas of biochemistry, enzymology and cell biology boosted the understanding of many rare endocrine, nutritional and metabolic diseases [38,39]. For these diseases, a missing or dysfunctional enzyme or substrate was discovered as the underlying cause [40,41] and has resulted in the development of a number of therapies that involve administration of the missing or dysfunctional enzyme or substrate [42]. For congenital malformations, however, the underlying cause might be an inherited (genetic) condition, toxic exposure of the foetus or birth injury, but in many cases, the cause is still unknown. Even if the cause is known, a therapy might not be feasible owing to the permanent nature of the defect, which involves the arrest, delay or misdirection of the development of a structure in embryonic life. Nonetheless, our results indicate that congenital malformations might benefit considerably from an increase in scientific research.

Disease-specific scientific output

For the association between the number of publications and a disease obtaining at least one product with a designation, the disease dataset was divided into three equal subgroups, based on the number of publications in the group of diseases without an orphan designation (Fig. 2). A disease for which more than 600 publications have been published had a twofold higher likelihood for obtaining at least one product with an orphan designation (adjusted OR = 2.23; 95%CI = 1.37–3.64) than a disease with less than 200 publications. The chance for a disease with from 200 to

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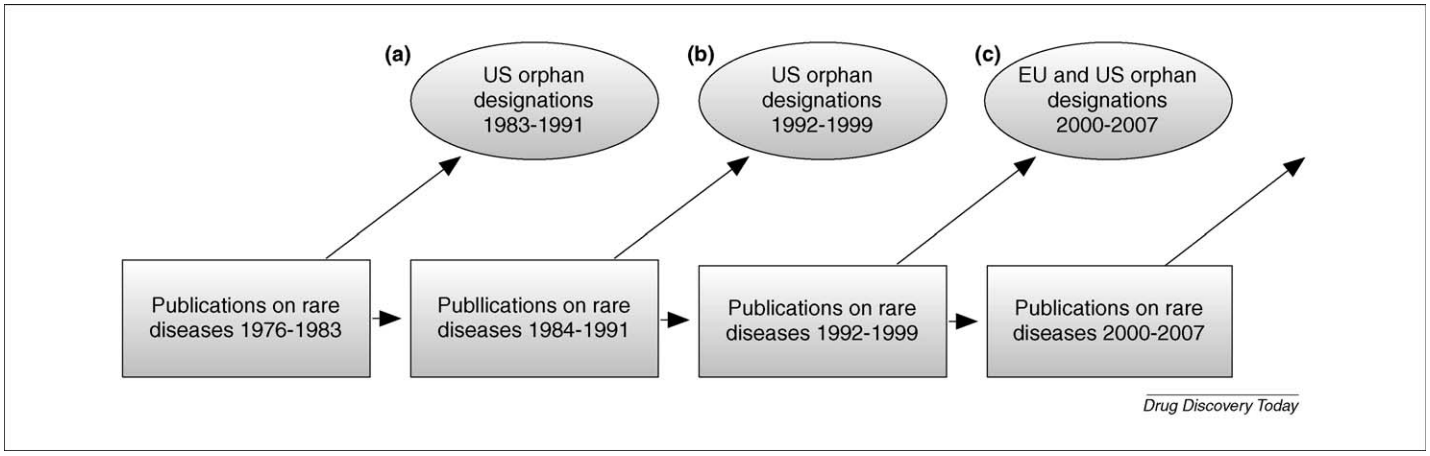

FIGURE 3

Publications on rare diseases and orphan designations. Depiction of the study design in which the association between the number of PubMed publications in one eight-year period and the likelihood of obtaining at least one product with an orphan designation in the next period was determined for the disease classes of oncological diseases; endocrine, nutritional and metabolic diseases; and congenital malformations. The results of these analyses are shown in Tables 1–3, respectively.

600 publications to obtain at least one product with an orphan designation did not differ from that of a disease with less than 200 publications. A secondary analysis by disease class further elucidated the influence of the number of publications within a disease class on the likelihood of a disease obtaining at least one product with an orphan designation. In this analysis, each disease class dataset was divided in two equal subgroups, based on the number of publications in the group of diseases without an orphan designation. Because the average number of publications per disease varied between disease classes, a many different number publications were used as a cut-off point for each disease class. An oncological rare disease with a high number of publications per disease (more than 1200) was found to be five times more likely to obtain at least one product with an orphan designation (OR = 5.20; 95%CI = 1.29–20.89) than an oncological disease with less than 1200 publications. In addition, endocrine, nutritional and metabolic diseases with a high number of publications (more than 200) were four times more likely to obtain at least one product with a designation (OR = 4.08; 95%CI = 1.50–11.08) than a disease with less than 200 publications in the same disease class. For diseases in other disease classes, we did not observe a statistically significant association between a high number of publications and obtaining at least one orphan designation. However, for the congenital malformations, a clearly increased (although not statistically significant) chance for obtaining at least one designation was found for a disease with more than 360 publications (OR = 2.60; 95%CI = 0.88–7.73). The effect became more pronounced when a cut-off point of 850 publications, representing the lowest number of publications of the upper quartile of the diseases without an orphan designation, was used (OR = 4.00; 95%CI = 1.45–11.05).

Finally, to exclude the possibility that the observed association was due to post-designation scientific output, the association between several publications in one eight-year period and the chance of obtaining at least one designation in the following eight-year period was analyzed (Fig. 3). Only disease classes for which a positive association was found between number of publications and obtaining at least one designation were included in the analysis. The results depicted in Tables 1–3 show that oncological diseases with a higher number of publications in each of the three periods (1976–1983, 1984–1991 and 1992–1999) had a higher

TABLE 1

Diseases with high and low number of publications between 1976 and 1983 for oncological diseases (*N* = 59), congenital malformations (*N* = 144) and endocrine, nutritional and metabolic diseases (*N* = 87) with and without at least one US orphan designation obtained in the next period (1983–1991)

	Number of diseases with at least one designation between 1983 and 1991 (US)	Number of diseases without designations between 1983 and 1991 (US)	OR (95%CI)
Oncological diseases			
Low number of publications (<200)	2	18	1 (reference level)
High number of publications (>200)	22	17	11.65 (2.37–57.23)
Endocrine, nutritional and metabolic diseases			
Low number of publications (<50)	0	40	1 (reference level)
High number of publications (>50)	9	38	NA
Congenital malformations			
Low number of publications (<50)	1	72	1 (reference level)
High number of publications (>50)	4	67	4.30 (0.47–39.44)

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TABLE 2

Diseases with high and low number of publications between 1984 and 1991 for oncological diseases (*N* = 59), congenital malformations (*N* = 144) and endocrine, nutritional and metabolic diseases (*N* = 87), with and without at least one US orphan designation obtained in the next period (1992–1999)

	Number of diseases with at least one designation between 1992 and 1999 (US)	Number of diseases without designations between 1992 and 1999 (US)	OR (95%CI)
Oncological diseases			
Low number of publications (<300)	2	18	1 (reference level)
High number of publications (>300)	23	16	12.94 (2.63–63.71)
Endocrine, nutritional and metabolic diseases			
Low number of publications (<75)	4	38	1 (reference level)
High number of publications (>75)	18	27	6.33 (1.93–20.83)
Congenital malformations			
Low number of publications (<75)	1	73	1 (reference level)
High number of publications (>75)	4	66	4.42 (0.48–40.59)

TABLE 3

Diseases with high and low number of publications between 1992 and 1999 for oncological diseases (*N* = 59), congenital malformations (*N* = 144) and endocrine, nutritional and metabolic diseases (*N* = 87), with and without at least one orphan designation obtained in the US or the EU during the next period (2000–2007)

	Number of diseases with at least one designation between 2000 and 2007 (US)	Number of diseases without designations between 2000 and 2007 (US)	OR (95%CI)
Oncological diseases			
Low number of publications (<400)	11	7	1 (reference level)
High number of publications (>400)	36	5	4.58 (1.21–17.35)
Endocrine, nutritional and metabolic diseases			
Low number of publications (<100)	15	31	1 (reference level)
High number of publications (>100)	22	19	2.39 (1.00–5.71)
Congenital malformations			
Low number of publications (<100)	3	64	1 (reference level)
High number of publications (>100)	13	64	4.33 (1.18–15.94)

chance of obtaining an orphan designation in the next period. The same applies to endocrine, nutritional and metabolic diseases with a high number of publications. For congenital malformations, a significantly higher chance for a disease with a high number of publications to obtain an orphan designation in the following period was only observed in the last eight-year period (1992–1999). In the following period (2000–2007), orphan designations were granted for 16 congenital malformations, of which 7 were granted by the EMEA, compared with 5 diseases with a designation in each of the 2 preceding periods. Qualitatively similar results were found for these three disease classes when publications of two consecutive eight-year periods (e.g. 1976–1991 or 1984–1999) were compared with obtaining a designation in the next eight-year period (1992–1999 or 2000–2007) (data not shown).

Thus, rare diseases with a high number of scientific publications are more likely to obtain a product with an orphan designation than rare diseases with a low number of publications. Interestingly, for congenital malformations, a significantly higher chance was observed for a disease with a high number of publications between 1992 and 1999 to obtain an orphan designation in the following eight-year period. An explanation for this observation, which is confirmed by several studies, could be that the elucidation of the human genome between 1990 and 2003 might have accelerated the identification of new genes causing certain congenital malformations [43,44]. Although the human genome project has brought about a great increase in the identification of disease-relevant genes and proteins, this has not yet resulted in the expected flood of new compounds, according to Lindsay [45]. Our finding indicates that the human genome project is not just paving the way for the identification of novel drug targets and better cell and animal models [45] but might also promote orphan drug development for congenital malformations.

Concluding remarks

This study has shown that successful translation of rare disease research into an orphan drug discovery and development programme is dependent on the disease class, the disease prevalence and the disease-specific scientific output. Previous studies have already shown the importance of pharmaceutical innovation for orphan drug discovery and development [13], and numerous analyses have amplified that the big challenge in the successful drug discovery and development lies in the translation of biomedical research into discovery and development of a successful product [15,26]. This translation incorporates the two-way process of using

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knowledge from basic research for the discovery and development of new methods for the treatment, prevention or diagnosis of diseases [15,46], involving industry and regulators, as well as academia [47]. Although the increase in biomedical research has sometimes been reported not to deliver the expected flood of new medicinal products [18,45], our study has shown that rare disease research really paves the way for new treatments that might provide a benefit to patients with a rare disease. Moreover, the observed close link between rare disease research and orphan drug development seems to substantiate the view of Tralau-Stewart *et al.* that industry needs academia and academia needs industry in future (orphan) drug discovery and development programmes [48]. Finally, these findings provide two important policy implications for further stimulating orphan drug development. First, the current orphan drug legislation is not sufficient to stimulate orphan drug development for diseases with a low prevalence or exceptionally rare diseases and, consequently, new (economic) incentives and other initiatives will be required. Pharmacy preparations, which have proven their added value in exceptionally rare disease management [49,50], public–private partnerships, such as the European Innovative Medicines Initiative (http://www.imi-europe.org; accessed June 2009) or the European Rare Diseases Therapeutic Initiative [51] and patient-initiated crowd-sourcing or open-source research, such as LAMsight (http://www.nytimes.com/2009/08/25/health/25web.html; accessed August 2009), might prove to be valuable developments in accomplishing this. Of course, future discussions on the details of supplementary orphan drug policies will have to include (public) costs. Second, a strong transnational research agenda on rare diseases is required to provide the necessary input for more orphan drug development programmes. This agenda should not merely focus on stimulating rare disorder research in general but should also focus on the specific needs at disease class level, in close interaction with patient organizations and learned societies. In this respect, the disease class of oncological diseases can serve as a valuable role model for other disease classes. The first step in Europe, which is already under way, will be to link national efforts [52] within a common European strategy for rare disease management with the aim of levering national research resources on rare diseases through synergistic cooperation and preparation of joint strategic activities (http://www.e-rare.eu; accessed April 2009). In the USA, the National Institutes of Health are already providing support for specific, preclinical research and product development for rare and neglected diseases (http://www.nih.gov/news/health/may2009/nhgri-20.htm; accessed June 2009).

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Attachment 3.

KA Burke, SN Freeman, MA Imoisili and TR Coté. **The Impact of the Orphan Drug Act on the Development and Advancement of Neurological Products for Rare Diseases: A Descriptive Review**. *Clin. Pharmacol. Ther.* 88:449-453, 2010.

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The Impact of the Orphan Drug Act on the Development and Advancement of Neurological Products for Rare Diseases: A Descriptive Review

KA Burke[1], SN Freeman[1], MA Imoisili[1] and TR Coté[1]

Many neurological diseases or conditions are rare disorders. The Orphan Drug Act (ODA) of 1983 was promulgated to promote the development of products for such conditions. In this Opinion piece, we discuss how the ODA has affected neurological diseases, note how current and future sponsors (any person(s) or entity (i.e., academic, corporate body, individual, manufacturer) that applies for an official regulatory action) of products for rare neurological diseases can take advantage of ODA incentives, identify areas of success and continuing needs, and review data that can help drive the future development of products for rare neurological conditions.

The 1983 Orphan Drug Act (ODA; Pub. L. no. 97-414) has had a tremendous impact on the availability and advancement of products for rare diseases and conditions.[1] This piece of legislation was put forth primarily to stimulate the development of products targeting rare diseases by lessening the economic burdens surrounding development. As a testament to the ODA's success, there have been several noteworthy advancements in the neurological field. Botox (botulinum toxin type A), originally approved for blepharospasm, strabismus, and cervical dystonia; Avonex (interferon-β1a), approved for multiple sclerosis; and Provigil (modafinil), approved for narcolepsy, are three examples of neurological orphan products that have achieved "blockbuster" status (annual sales exceeding US$1 billion worldwide). Although many successes may be directly attributable to the ODA, of the 6000–7000 rare diseases, only approximately16 neurological diseases have an approved treatment on the market, highlighting the need for further efforts. To address the impact of the ODA on the development and advancement of orphan products for rare neurological disorders, we provide a descriptive review of all designated and approved products and discuss possible future directions.

Per the ODA, the Office of Orphan Products Development (OOPD) within the US Food and Drug Administration (FDA) grants an *orphan designation* to any product indicated for a rare disease or condition; defined as a disease affecting fewer than 200,000 persons in the United States or more than 200,000 if there is "no reasonable expectation that the costs of drug development and marketing will be recovered in future sales of the drug in the United States" (21 CFR 316.10 (b)(8)(ii)). An application will not receive an orphan designation if, among other reasons, there is insufficient information indicating that the drug is useful for the rare disease(s) (21 CFR 316.14 (a)(2)(iii)). The rules for granting designations (operated by OOPD) are less stringent than those for marketing approval (operated by the review divisions). An orphan designation can be granted at any point during the development process. Data presented must contain sufficient information that supports the effectiveness of the use of a particular product of interest in the proposed indication based on the clinical investigations conducted by the sponsor. A preclinical study utilizing an animal model is also acceptable as long as an adequate animal model of the disease or condition is selected to support the expectation that the drug would be effective in the prevention, diagnosis, or treatment of the disease or condition. The use of *in vitro* studies involving a demonstration of the mechanism of action of the product and/or a meaningful illustration of the pathogenesis of the disease may also be suitable.

An orphan-designated product may receive marketing approval if data derived from subsequent clinical trials demonstrate product safety and efficacy. (A marketing approval indicates that the

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FDA (review division) has determined, following a review of data derived from clinical studies, that the product is safe and effective.) Orphan designation (a determination of product promise for rare diseases/conditions) can be granted at any time during the drug/biologic development process until the submission of a marketing application for that orphan indication (21 CFR 316.23(a)). The data are submitted in form of a New Drug Application (NDA) for drugs, or a Biologic License Application (BLA) for biological products. (Note that small molecules will be referred to as drugs; therapeutic agents synthesized from living organisms will be referred to as biologics.)

An orphan product designation confers certain benefits for a sponsor of a newly approved product. These include 50% tax credits for clinical development costs, exemption from NDA/BLA application user fees, and market exclusivity for seven years (Pub. L. no. 97-414). Another incentive is the opportunity to apply for grants for product development through the OOPD. Additionally, all orphan-designated products are exempt from requirements contained in the Pediatric Research Equity Act of 2007. (In this act, the agency may require pediatric studies for new drug/biological product applications if the product is likely to be used in pediatric patients.) The aforementioned incentives have had a dramatic impact on the development of drug and biologic products for rare disease. In the decade before 1983, only 10 products for rare diseases received a marketing approval.[2] Since the passage of ODA through 2009, 346 of 2,112 orphan-designated products have been approved—an average of about 13 products per year—constituting a significant advancement for these underserved patient populations. As the ODA continues to attract and open new avenues to academic scientists, as well as biotech and pharmaceutical companies, in the development of therapies for rare diseases, the number of designations and approvals for all fields, including neurology, is likely to steadily increase.

An overview of achievements regarding orphan designations and marketing approvals for orphan neurological products (drugs and biologics) is provided in Table 1. A staff neurologist in the OOPD classified all products using information from the FDA Internal Orphan Products Database. Products classified as neurological were defined as those intended to treat diseases affecting the central or peripheral nervous systems. Excluded from our list were products developed to treat rare cancers of the nervous system and inborn errors of metabolism because these diseases are not primarily neurological in nature (and thus are reviewed by separate divisions within the FDA).

On the basis of these criteria, 205 of the total 2,112 orphan designations from 1983 through 2009 (~10%) were identified as neurological products (Table 1). Of these 205 neurological orphan products, 27 (13%) received marketing approval. Table 1 illustrates these designations and marketing approvals by category. Products designed to treat similar rare neurological diseases or conditions were placed in one of the categories listed in the table. Products that did not clearly fit into one of the categories or had indications that spanned two or more categories were placed in the miscellaneous category. Products designated for neurodegenerative or movement disorders constituted the largest group, receiving 71 (35%) of the 205 orphan designations. Furthermore, products for specific diseases within this category tended to receive the largest number of orphan designations. Amyotrophic lateral sclerosis (ALS) therapeutics received 26 (10% of all neurological designations), followed by Huntington's disease (HD), with 15 (7%). Products for the treatment of multiple sclerosis had 14 orphan designations (7%), and those for Parkinson's disease received 9 (4%). Among the other five categories, 49 (24%) of the 205 total orphan designations were for neurodegenerative/movement disorders, 19 (9%) were for head/spinal trauma disorders, 19 (9%) were for seizure disorders, 16 (8%) were for pain disorders, and 9 (4%) were for sleep disorders. Products designated for diseases in the miscellaneous category consisted of 22 (11%) of a total of 205 designations (Table 1).

In addition to receiving the largest percentage of designations, products for neurodegenerative diseases received the most marketing approvals as well. Among the 27 marketing approvals, 10 (37%) were for neurodegenerative disorders. This category was followed by seizure disorders, with 7 marketing approvals (26%); nonneurodegenerative disorders, with 4 (15%); sleep disorders, with 3 (11%); pain disorders, with 2 (7%); and miscellaneous disorders, with 1 (4%) (Table 1).

Figure 1 illustrates trends in all neurological orphan product designations and marketing approvals. As shown, there has been a considerable increase

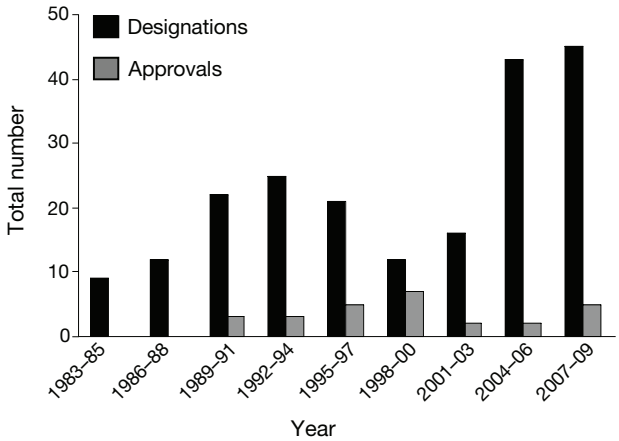

Figure 1 Orphan designations and marketing approvals for neurological products (1983–2009). The total number of orphan designations (black) and marketing approvals (gray) awarded for rare neurological diseases in 3-year increments between 1983 and 2009.

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Table 1 Orphan-designated neurological products (1983–2009)

Classification	Orphan indications	Orphan designations	Marketing approvals
Movement disorders (neurodegenerative)	Amyotrophic lateral sclerosis	26	1
	Huntington's disease	15	1
	Multiple sclerosis[a]	14	5
	Parkinson's disease[a]	9	2
	Friedreich's ataxia	2	0
	Progressive supranuclear palsy	2	0
	Chronic inflammatory demyelinating polyneuropathy	1	1
	Familial amyloid polyneuropathy	1	0
	Tay–Sachs disease	1	0
Subtotal		**71**	**10**
Movement disorders (nonneurodegenerative)	Spinal muscle atrophy	8	0
	Duchenne muscular dystrophy	7	0
	Cervical dystonia/dystonia	5	2
	Duchenne/Becker muscular dystrophy	3	0
	Pediatric cerebral palsy/muscle contracture	4	0
	Blepharospasm/dystonia	3	1
	Lambert–Eaton myasthenic syndrome	3	0
	Myasthenia gravis	2	0
	Tardive dyskinesia	2	0
	Alternating hemiplegia	1	0
	Cataplexy	1	0
	Congenital muscular dystrophy	1	0
	Cranial nerve aberrant regeneration/eyelid closure	1	0
	Familial spastic paraparesis	1	0
	Hyperekplexia	1	0
	Multifocal motor neuropathy	1	0
	Muscular dystrophy	1	0
	Myotonic muscular dystrophy	1	0
	Pathological drooling in pediatric patients	1	0
	Strabismus/dystonia	1	1
	Stiff-person syndrome	1	0
Subtotal		**49**	**4**
Head/spinal trauma	Spinal cord injury (including acute)	4	0
	Vasospasm/subarachnoid hemorrhage	3	0
	Closed-head brain injury	2	0
	Spinal cord injury (neuropathic pain)	2	0
	Severe head injury	2	0
	Severe traumatic brain injury	2	0
	Incomplete spinal cord injury	1	0
	Spinal cord injury (neurological outcomes)	1	0
	Spinal cord injury (sexual dysfunction)	1	0
	Severe to moderate traumatic brain injury (neurological sequelae)	1	0
Subtotal		**19**	**0**
Seizure	Lennox–Gastaut syndrome	5	4
	Bouts of increased seizure/acute repetitive seizures/seizure clusters in epilepsy patients	4	1
	Infantile spasms	3	1
	Myoclonus (postanoxic and symptomatic)	3	0
	Status epilepticus, grand mal type seizure	3	1
	Drug-resistant generalized tonic-clonic epilepsy	1	0
Subtotal		**19**	**7**
Pain	Postherpetic neuralgia	7	1
	Painful HIV-associated neuropathy	4	0
	Trigeminal neuralgia	2	0
	Allodynia and postherpetic neuralgia	1	1
	Severe reflex sympathetic dystrophy and causalgia	1	0
	Trigeminal neuralgia and postherpetic neuralgia	1	0
Subtotal		**16**	**2**
Sleep	Narcolepsy (with and without auxiliary symptoms)	6	3
	Circadian rhythm sleep disorders (blind patients)	2	0
	Non-24-hour sleep/wake disorder (blind patients)	1	0
Subtotal		9	3

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Table 1 Continued

Miscellaneous	Spasticity due to spinal cord injury or multiple sclerosis	4	1
	Charcot–Marie–Tooth disease	2	0
	Guillain–Barré syndrome	2	0
	Postpoliomyelitis syndrome	2	0
	Tuberous sclerosis complex	2	0
	Acute sensorineural hearing loss	1	0
	Adjunct/microsurgical peripheral nerve repairs	1	0
	Herpes zoster in immunocompromised patients	1	0
	HIV-associated sensory neuropathy	1	0
	Mitochondrial disease	1	0
	Hunter syndrome (neurocognitive symptoms)	1	0
	Neurogenic symptomatic orthostatic hypotension in patients with autonomic failure, dopamine-β-hydroxylase deficiency and nondiabetic autonomic neuropathy	1	0
	Niemann–Pick (type C) (neurological manifestations)	1	0
	Osmotherapy for intracranial hypotension/cerebral edema	1	0
	Subacute sclerosing panencephalitis	1	0
Subtotal		**22**	**1**
Total		**205**	**27**

Products for diseases or conditions were classified on the basis of similar variables and characteristics. Thus, these products fell into the following groups: movement disorders (neurodegenerative and nonneurodegenerative), head and spinal trauma, seizure, pain, sleep, and miscellaneous.

[a]Although the Office of Orphan Products Development grants orphan designations for medically plausible subsets of diseases, Parkinson's disease and multiple sclerosis patients are considered to exceed 200,000 in the United States.

in the total number of designated and approved products from 2000 to 2009. Remarkably, 108 (53%) of the 205 designations and 13 (48%) of the 27 marketing approvals for neurological products were granted in these ten years (2000–2009). Furthermore, 45 (22%) of the neurological orphan designations were granted in the last three years. This could mark a trend of further increases in the total number of approvals in the next decade, in that the average time between orphan designation and marketing approval (for products that receive marketing approval) is approximately four years.[3]

Since the passage of the ODA, the number of orphan designations and marketing approvals for neurological rare diseases has risen dramatically. The considerable achievements in the past 27 years are clearly due to advancements in this field, especially within neurodegenerative diseases. Approximately 71 (35%) and 10 (37%) products have been designated and have received marketing approvals, respectively, for this class of diseases. Although this constitutes a significant advancement for these small patient populations, there remain a substantial number of other neglected neurodegenerative diseases that have no treatments. Furthermore, of those rare neurodegenerative diseases for which treatments have been approved, most products available for use so far provide only symptomatic relief; there is no evidence that they slow the progression of the underlying disease process. In rare cases, they minimally prolong life. For example, orphan designations for both ALS and HD comprise over 50% of all designations for neurodegenerative diseases and yet only have one marketing approval each, i.e., riluzole (Rilutek), which was approved in 1992 for ALS, and tetrabenazine (Xenazine), approved in 2008 for HD. Although these two drugs have shown some benefit for these suffering patient populations, the treatments associated with these products are not curative. Thus, there remains a critical need for sponsors to develop more and improved products, not only for ALS and HD but for the entire neglected rare neurological diseases overall. To further stimulate the development of products for rare diseases, the OOPD has provided a "rare disease repurposing database" on its website. Patients with certain rare diseases (e.g., cystic fibrosis) have benefited from new therapies derived from preexisting products. Literature is replete with similar examples in oncology, infectious diseases, and other areas. Neurological rare diseases could also benefit from this rationale. Repurposing of previously approved products (already considered safe in other conditions) could facilitate development if found effective for a rare neurological condition.

Although small molecules and biologics continue to be an active area of research, other strategies are being pursued. Given the pathology of these complex diseases, the necessity of the replacement or regeneration of damaged neurons has been recognized. As such, stem cell–based products have manifested themselves as promising new therapeutics. In this strategy, adult or human embryonic stem cells are procured and induced to differentiate into the desired neural precursors or terminally differentiated neurons *ex vivo*. These cells are subsequently introduced for the purpose of providing new neurons to compensate for those that have been lost, regenerating lost myelin, providing factors to induce cell growth, and/or regulating inflammatory responses.[4] Although traditional therapies remain the status quo, it is apparent that stem cell–based products are maturing toward potential clinical use in neurological diseases.

The ODA has had a profound effect on the development of products for rare

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diseases. Additionally, this act has provided a platform to aid sponsors in the development of products to treat rare diseases both within and outside the field of neurological diseases. Given these results, we believe that there is ample room for academic researchers, in addition to pharmaceutical and biotech sponsors, to further partake in the development of products for rare neurological disorders. Thus, with added participation, we hope to see the number of drug/biologic marketing approvals increase for the benefit of these neglected populations.

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CONFLICT OF INTEREST
The authors declared no conflict of interest.

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Attachment 4.

P Zhao, L Zhang, JA Grillo, Q Liu, JM Bullock, et al. **Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review.** Clin Pharmacol Ther. 89(2):259-267, 2011.

Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

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Physiologically based pharmacokinetic (PBPK) modeling and simulation is a tool that can help predict the pharmacokinetics of drugs in humans and evaluate the effects of intrinsic (e.g., organ dysfunction, age, genetics) and extrinsic (e.g., drug–drug interactions) factors, alone or in combinations, on drug exposure. The use of this tool is increasing at all stages of the drug development process. This report reviews recent instances of the use of PBPK in decision-making during regulatory review. The examples are based on Center for Drug Evaluation and Research reviews of several submissions for investigational new drugs (INDs) and new drug applications (NDAs) received between July 2008 and June 2010. The use of PBPK modeling and simulation facilitated the following types of decisions: the need to conduct specific clinical pharmacology studies, specific study designs, and appropriate labeling language. The report also discusses the challenges encountered when PBPK modeling and simulation were used in these cases and recommends approaches to facilitating full utilization of this tool.

Physiologically based pharmacokinetic (PBPK) models estimate the pharmacokinetic (PK) profile or exposure in "a target tissue or organ after a drug dose by taking into account the rate of absorption into the body, distribution among target organs and tissues, metabolism, and excretion" (http://www.epa.gov/opp00001/science/comptox-glossary.html#p). The development of PBPK models can be traced back to 1937, when Teorell derived several formulas to describe drug concentrations over time in blood and tissues.[1] Although his model was a rudimentary one, its emphasis on drug distribution and concentration as a function of time in tissues other than blood make this probably the first PBPK model. For several decades, efforts have been made to refine PBPK models that can be applied in drug development and the evaluation of environmental toxins (ref. 2 and the references therein). Over the past two decades, the advancements in computer science and the explosion of knowledge in biomedical sciences supported development of the highly sophisticated, population-based PBPK modeling and simulation tools that are now available.[3–6]

An important role of clinical pharmacologists is to identify optimal dosing regimens for individual patients. In order to achieve this, the effects of intrinsic (e.g., organ dysfunction, age, genetics) and extrinsic (e.g., drug–drug interactions) patient factors (**Figure 1a**) on drug exposure and response need to be evaluated during drug development.[7] PBPK modeling and simulation can help predict the pharmacokinetics of drugs in humans, including the effect of intrinsic and extrinsic factors on ADME (absorption, distribution, metabolism, and excretion). These predictions aid in the selection of optimal dosing regimens. **Figure 1b** illustrates components of a PBPK model, including drug-dependent and drug-independent system components. The system components are based on decades of knowledge of body fluid dynamics (e.g., secretion of gastric acid and bile, blood flow, urine flow), tissue size and composition, abundance and distribution of drug receptors, drug-metabolizing enzymes, and membrane transporters in various organ and tissue compartments. The drug-dependent component of the model enables the study of ADME processes and mechanisms of action at the cellular level by dividing the organs into tissue and intracellular spaces. Consequently, changes in the magnitude and time course of drug exposure and drug action in the tissue of interest can be investigated.

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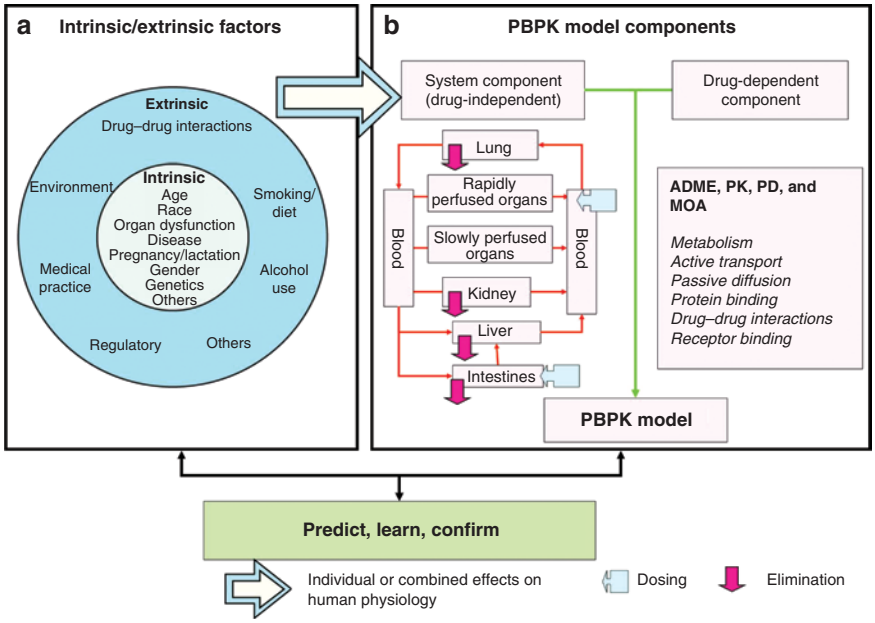

The degree of complexity of the PBPK model can vary according to the need.

Figure 1 Application of physiologically based pharmacokinetic (PBPK) modeling and simulation to evaluate the effect of various extrinsic and intrinsic factors on drug exposure and response. (**a**) Intrinsic and extrinsic patient factors that can affect drug exposure and response (taken from Huang and Temple[7]). (**b**) Components of PBPK modeling (drug-dependent component and drug-independent (system) component). The figure indicates that the effects of individual or combined intrinsic/extrinsic factors on drug exposure are projected via both drug-dependent and drug-independent (system) components of the PBPK model. ADME, absorption, distribution, metabolism, and excretion; MOA, mechanism of action; PD, pharmacodynamics; PK, pharmacokinetics.

Publications in the literature describe the use of PBPK modeling in critical areas of clinical pharmacology, including pediatrics,[8–11] formulation effect,[12,13] organ impairment,[14,15] and drug–drug interactions.[16–21] The dynamic models that incorporate interindividual variability of intrinsic factors can help determine optimal dosing regimens and sampling schemes at the time of designing clinical pharmacology studies.[16,19,21–24]

From July 2008 to June 2010, the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research of the US Food and Drug Administration (FDA) used PBPK modeling and simulation while reviewing numerous submissions to assist in several types of decisions relating to the need to conduct specific clinical pharmacology studies (both premarketing and postmarketing), the design of the studies, and the appropriate language in the labeling. In this report, we provide a summary of these submissions and their regulatory implications, and we present lessons learned from these reviews.

RESULTS

Summary of PBPK modeling and simulations included in IND and NDA submissions

From July 2008 to June 2010, the FDA reviewed seven investigational new drug (IND) and six new drug applications (NDA) submissions containing PBPK modeling and simulations conducted by the sponsors. In addition, FDA reviewers conducted PBPK modeling and simulations to support clinical pharmacology reviews of another four NDA submissions for which the sponsors did not use PBPK. As a comparison, in the 3 years before 2008, FDA received only two submissions containing PBPK modeling and simulations. Many of the PBPK modeling and simulation evaluations addressed questions relating to drug–drug interactions; others addressed pediatric dosing, the impact of hepatic impairment on drug exposure, and the impact of multiple factors on drug exposure (**Table 1**). A scheme of PBPK modeling and simulations can be generalized to include five basic steps, as outlined in **Figure 2**. In step 1, the drug's clearance pathways are identified and quantified. In step 2, drug-dependent parameters are incorporated into PBPK models. Step 3 compares the predicted concentration–time profiles with those obtained from available *in vivo* human studies. Step 4 consists of refining the model on the basis of the results from step 3. Finally, in step 5, the refined PBPK model is used for predicting PK profiles under various scenarios that have not been studied experimentally. In addition, the mean and upper/lower boundaries that reflect variability or uncertainty are simulated.

Four case studies that posed different regulatory questions regarding the use of PBPK modeling and simulation are described in the following sections of this report.

Representative case studies

Case 1. Specific regulatory question: Can PBPK simulations rule out CYP2C9 inhibition by drug A, even though the ratio of *in vivo* inhibitor concentration (*I*: maximum plasma concentration at the highest proposed dose) to *in vitro* inhibition constant (K_i) of CYP2C9 (I/K_i) is >0.1?

Synopsis: *In vitro* drug interaction data indicate that drug A is a reversible inhibitor of CYP2C9, with an estimated I/K_i ratio of ~2, where *I* is the maximal plasma concentration of drug A. The 2006 draft FDA drug interaction guidance indicates that a clinical drug interaction study should be conducted when the

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Table 1 Summary of general regulatory questions addressed using PBPK modeling and simulations

Cases	Main enzymatic pathways; interacting drug/substrate relationships	Regulatory questions addressed related to PBPK modeling and simulations
1	NME is a CYP inhibitor *in vitro* ($I/K_i > 0.1$)	Can PBPK simulations predict the magnitude of DDI with a CYP substrate *in vivo*?
2	NME is a CYP substrate	An *in vivo* DDI study with a CYP inhibitor has been conducted when NME was dosed orally. Can PBPK simulation predict the magnitude of DDI when NME is given intravenously?
3	NME is a CYP substrate and also renally excreted	Can PBPK simulations predict the magnitude of DDI in subjects with varying degrees of renal impairment (mild, moderate, or severe)?
4	NME is a CYP inhibitor *in vitro* ($I/K_i > 0.1$) NME is metabolized by multiple CYPs in the liver	Can PBPK simulations predict the magnitude of DDI with a CYP substrate *in vivo*? Can PBPK simulations predict the magnitude of DDI with CYP inhibitors? Can PBPK simulations predict PK in subjects with hepatic impairments?
Others	NME is a substrate of a polymorphic CYP *in vitro*	Can PBPK simulations predict the PK in extensive, intermediate, or poor metabolizers of this CYP?
	NME is a CYP substrate and a DDI study using a specific inhibitor dose has been conducted *in vivo*	Can PBPK simulations predict the magnitude of DDI using a different inhibitor dose as recommended by the FDA?
	NME is a CYP substrate and an *in vivo* DDI study has been conducted with a CYP inhibitor	Can PBPK simulations predict the magnitude of DDI with a CYP inducer?
	NME is a TDI of a CYP	Its single-dose PK data are available: Can PBPK simulations predict dose- and time-dependent PK after multiple dosing? Can PBPK simulations predict TDI *in vivo*?
	NME is metabolized by multiple CYPs	Can PBPK simulation be used to predict fractional metabolism based on enzyme kinetic studies *in vitro*?
	NME's adult PK data are available	Can PBPK simulations help determine the optimal doses for pediatric studies?
	NME is metabolized in the liver	*In vivo* data are available in hepatically impaired subjects taking lower than recommended doses of NME. Can PBPK simulations predict PK of NME in hepatic impairment patients taking recommended doses?
	NME and its metabolite are both inhibitors of a CYP	Can PBPK simulation predict the DDI potential of the NME?

CYP, cytochrome P450; DDI, drug–drug interactions; FDA, US Food and Drug Administration; NME, new molecular entity; PBPK, physiologically based pharmacokinetic; PK, pharmacokinetic; TDI, time-dependent inhibitor.

I/K_i ratio is >0.1 (ref. 25). The sponsor's PBPK simulations indicated that because drug A has a short half-life, there would be minimal drug interaction with the CYP2C9 substrate warfarin. The FDA's PBPK analysis included metabolites in the model. These metabolites have longer half-lives and higher systemic exposure than drug A does (e.g., the AUC of one metabolite is 10-fold higher than that of drug A). The inhibition potential of the metabolites is not known. The FDA's PBPK model used a conservative approach, assuming the same inhibition potency for metabolites as for the parent drug. The resulting PBPK simulation suggested that coadministration of drug A can inhibit CYP2C9 and increase the exposure of warfarin.

Conclusion: PBPK modeling does not rule out the potential for drug A to inhibit the metabolism of a CYP2C9 substrate. Although PBPK simulation may provide more information than the I/K_i ratio, the lack of metabolite inhibition data limited the utility of the PBPK simulation in this specific case. The sponsor is conducting *in vitro* inhibition studies of the metabolites and will incorporate the data in the PBPK model. If the PBPK model that includes actual metabolite inhibition data indicates that administration of drug A does not significantly inhibit metabolism of a CYP2C9 substrate, an *in vivo* interaction study between drug A and warfarin may not be needed. However, if the model indicates significant inhibition of CYP2C9, a clinical study of the interaction between drug A and warfarin is warranted.

Case 2. Specific regulatory question: Can PBPK modeling and simulation predict the magnitude of interaction between a strong CYP3A inhibitor and a sensitive CYP3A substrate administered intravenously, on the basis of the data from an interaction study between the inhibitor and the substrate administered orally?

Synopsis: Sildenafil is a sensitive CYP3A substrate that undergoes significant first-pass metabolism. After oral administration, 92% of the drug was absorbed with an absolute bioavailability of 38%.[26] It is also metabolized by CYP2C9. Oral administration of sildenafil with ritonavir, a strong CYP3A inhibitor, resulted in a greater than 10-fold increase in sildenafil AUC. In order to predict the magnitude of interaction between ritonavir (or other strong CYP3A inhibitors) and sildenafil administered intravenously, the sponsor constructed a PBPK model for sildenafil and ritonavir, and conducted simulations for the new administration route of sildenafil. The results indicated a smaller degree of drug interaction (AUC increased by approximately threefold) when sildenafil is given intravenously vs. orally. The smaller magnitude of interaction with intravenous administration as compared with oral administration of sildenafil is expected and is consistent with literature data for midazolam, another CYP3A-sensitive substrate with significant first-pass metabolism. Data in the literature comparing drug interactions of midazolam after oral and intravenous administration in the presence and absence of a strong CYP3A inhibitor showed a

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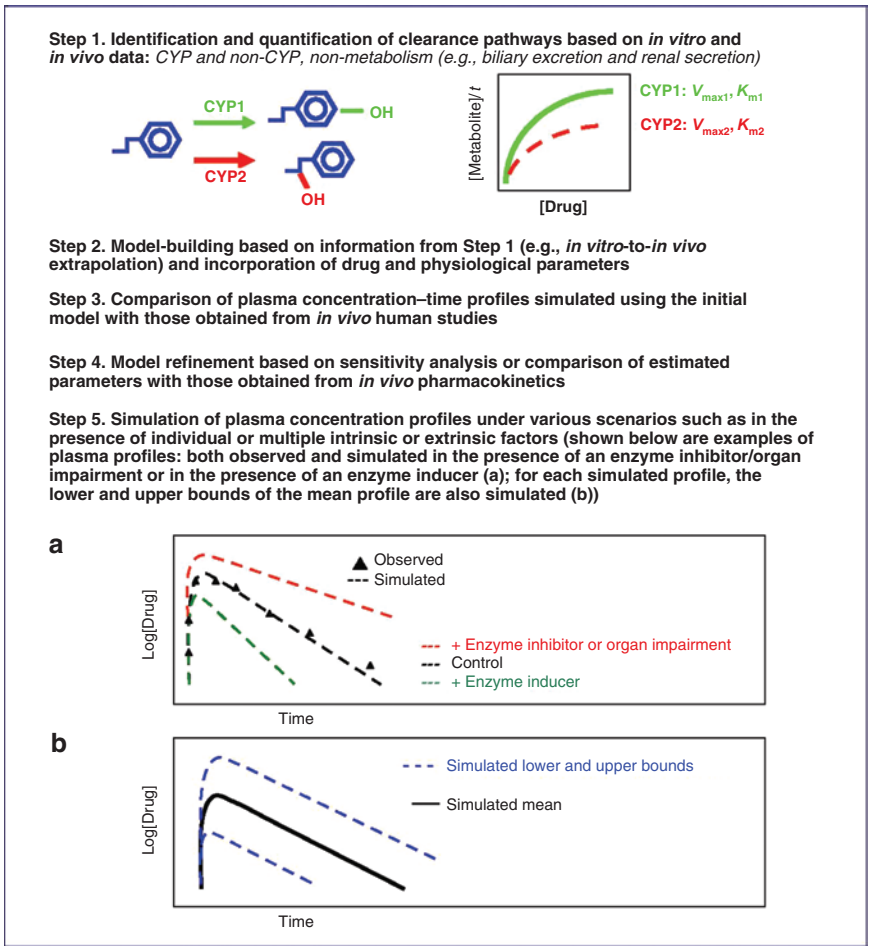

Figure 2 General processes in PBPK modeling and simulations. CYP1 and CYP2 represent two CYP isoforms involved in the metabolism of the new molecular entity (NME); CYP, cytochrome P450; K_m, Michaelis–Menten constant; V_{max}, maximum rate of reaction; [Metabolite] and [Drug], concentrations of metabolite and substrate drug.

decreased extent of inhibition after intravenous administration of the substrate as compared to oral administration of the substrate (Table 2).

The FDA's independent PBPK analysis also indicated that the magnitude of the effect of a strong CYP3A inhibitor on sildenafil concentrations is smaller when sildenafil is administered intravenously as compared with when it is administered orally (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022473s000_ClinPharmR.pdf). However, the quantitative effect of ritonavir on intravenously administered sildenafil cannot be confirmed because of two potential limitations. First, the contribution of CYP3A to the overall clearance of sildenafil ($f_{m,CYP3A}$) cannot be confirmed. *In vitro* data showed that CYP3A and CYP2C9 contributed 80% and 20%, respectively, to the formation of UK-103,320, a metabolite of sildenafil. These data were used in the sponsor's PBPK model to represent the metabolism of sildenafil. However, several primary metabolites including UK-103,320 have been reported *in vivo*.[26] Therefore, the *in vitro* f_m values calculated based on UK-103,320 formation may not represent the *in vivo* contribution to sildenafil metabolism by each CYP isoform. Because the magnitude of drug–drug interaction is influenced by f_m,[27] confirmation of $f_{m,CYP3A}$ is critical. Second, the PBPK model did not consider concurrent induction of CYP3A by ritonavir.[28] As the induction of CYP3A by multiple doses of ritonavir may offset the strong CYP3A inhibition effect of the drug, accurate prediction of the magnitude of the drug–drug interaction between ritonavir and intravenous sildenafil would need to consider both induction and inhibition in the model. Therefore the magnitude of drug–drug interaction may depend on the dosing regimen (e.g., duration of pretreatment) of ritonavir.

Conclusion: On the basis of the PBPK model and the midazolam drug interaction literature, the FDA agreed with the sponsor's conclusion that a smaller degree of drug–drug interaction is anticipated between a strong CYP3A inhibitor and sildenafil when the latter drug is administered intravenously as compared to oral administration. It was therefore found to be acceptable to include the following wording in the sildenafil injection product label: "Predictions based on a pharmacokinetic model suggest that drug–drug interaction with CYP3A inhibitors will be less than those observed after oral sildenafil administration." However, several limitations prevent the use of PBPK modeling to determine the quantitative effect of the interaction between ritonavir and the sildenafil injection product.

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Table 2 Summary of PK parameters of midazolam and sildenafil with and without coadministration of CYP3A inhibitors (clarithromycin, ketoconazole, ritonavir, saquinavir, or erythromycin)

	PK parameters				AUCR (± inhibitor)		
	CL_{iv} (L/h)	F_{oral}	F_g	F_h	p.o.	i.v.	Reference
Midazolam	27.8	0.31	0.42	0.74	—	—	Gorski[42], 1998[a]
Midazolam+clarithromycin	10.1	0.75	0.83	0.90	7.0	2.7	Gorski[42], 1998
Midazolam+ketoconazole (200 mg)	—	—	—	—	11.0	3.4	Lucksiri[43], 2005[b]
Midazolam+ketoconazole (400 mg)	—	—	—	—	15.0	4.2	Lucksiri[43], 2005
Sildenafil	40.8	0.38	0.69	0.55	—	—	Muirhead[26], 2002a[c]
Sildenafil+ritonavir	—	—	—	—	11	—	Muirhead[44], 2000[d]
Sildenafil+saquinavir	—	—	—	—	3.1	—	Muirhead[45], 2000
Sildenafil+erythromycin	—	—	—	—	2.6	—	Muirhead[45], 2002b[e]

AUCR: AUC ratio = $AUC_{with\ inhibitor}/AUC_{without\ inhibitor}$.

F_g, bioavailability in the gut; F_h, bioavailability in the liver; F_{oral}, oral bioavailability.

[a]Gorski 1998: i.v. and p.o. midazolam was given before and on day 7 of oral clarithromycin (500 mg b.i.d. day 1–7). [b]Lucksiri 2005: i.v. and p.o. midazolam was given before and during 7-day oral ketoconazole (200 or 400 mg q.d., i.v. midazolam on day 6, p.o. midazolam on day 7). [c]Muirhead 2002(a): i.v. sildenafil 25 mg; p.o. sildenafil 50 mg. Blood pharmacokinetic parameters were calculated. Complete absorption and predominant liver metabolism after i.v. administration were assumed. [d]Muirhead, 2000: p.o. sildenafil before and on day 6/7 of b.i.d. oral ritonavir (300 mg b.i.d. on day 1, 400 mg b.i.d. on day 2, and 500 mg b.i.d. on days 3–7), or p.o. sildenafil before and on day 6/7 of oral saquinavir (1,200 mg t.i.d.). [e]Muirhead, 2002(b): p.o. sildenafil before and on day 5 of b.i.d. oral erythromycin (500 mg).

Case 3. Specific regulatory question: Can PBPK modeling and simulation determine the combined effect of multiple factors (e.g., moderate renal impairment + moderate enzyme inhibitor)?

Synopsis: Rivaroxaban is an orally administered direct factor X_a inhibitor approved in Europe for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. The product information (SmPC) and public assessment report (EPAR) is available on the EMA homepage (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000944/human_med_001155.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125). Rivaroxaban is eliminated via two major routes: (i) ~36% of the dose is excreted renally as unchanged drug, with net secretion (likely mediated by P-glycoprotein and/or breast cancer-resistant protein) and filtration contributing at a ratio of approximately 5:1 and (ii) hepatic metabolism by CYP3A (~18%), CYP2J2 (~14%), hydrolysis (~14%), and an uncharacterized pathway (~8%). Coadministration of rivaroxaban with ketoconazole or other strong CYP3A/P-glycoprotein inhibitors such as ritonavir resulted in an increase in rivaroxaban AUC by ~2.5-fold, which is considered clinically relevant. However, studies with other inhibitors such as erythromycin and clarithromycin reported 1.3- and 1.5-fold increases in rivaroxaban AUC, respectively; these were not deemed clinically relevant. The sponsor considered erythromycin to be a weak-to-moderate CYP3A4/P-gp inhibitor and clarithromycin to be a strong CYP3A4 /weak-to moderate P-gp inhibitor in these studies. Further, the PK of rivaroxaban was evaluated in subjects with renal impairment, as estimated by creatinine clearance (CL_{Cr}). As compared with the corresponding values in healthy volunteers (CL_{Cr} > 80 ml/min), rivaroxaban AUC values were increased 1.4- to 1.6-fold in subjects with values of CL_{Cr} down to 15 ml/min (EMA Review). The EMA review and Summary of Product Characteristics noted that rivaroxaban was not recommended in patients with severe renal impairment (CL_{Cr} < 15 ml/min), that the changes in exposure in patients with mild to moderate renal impairment were not deemed clinically relevant, and that severe renal impairment with CL_{Cr} of 15–29 ml/min required that caution be exercised while prescribing the drug regimen. It was considered important to address the question of whether a combination of factors (e.g., mild to moderate renal impairment plus concomitant administration of a mild to moderate CYP3A4 inhibitor)—each of which by itself would not be deemed clinically relevant—could result in a clinically relevant change in rivaroxaban exposure.

To project the extent of drug–drug interaction in patients with various degrees of renal impairment and who are on a regimen of rivaroxaban with CYP/efflux transporter inhibitors, the reviewers constructed a semi-PBPK model. The utility and the associated designs of semi-PBPK models have been reviewed elsewhere[19,20,29,30] and are not discussed in detail here. Confidence in the final model was assessed by visual comparison of simulated rivaroxaban plasma concentration-vs.-time profiles with those observed from clinical studies[31] in which the drug had been administered in a similar manner.

The semi-PBPK model evaluated drug–drug interaction at the organ level (liver and kidney), and the effect of renal impairment, using a time-based inhibitor concentration model. In addition, the model considered concurrent inhibition of hepatic CYP enzymes and kidney efflux transporter(s) and the possible effect of renal impairment on hepatic enzyme activity.[32,33] Because the absolute oral bioavailability of rivaroxaban is nearly 100% (EMA Review), first-pass metabolism and efflux transport in the gut wall were not considered in the model.

The effect of erythromycin on the elimination of rivaroxaban was then evaluated. The inhibition of the renal secretion of rivaroxaban by efflux transporters and the CYP2J2-mediated

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elimination pathway were assumed to be reversible, whereas inhibition of CYP3A4 was assumed to be time-dependent (or irreversible inhibition in the presence of erythromycin, http://www.druginteractioninfo.org, accessed July 2010). Next, using the semi-PBPK model, the reviewers assessed the effect of coadministration of erythromycin along with rivaroxaban in subjects with renal impairment.

The model predicted that, as renal function decreased by 0% (no impairment), 25%, 50%, 75%, and 90%, the rivaroxaban exposure (AUC) in the presence of erythromycin would increase by 1.2-, 1.5-, 2.0-, 3.0-, and 4.1-fold, respectively, as compared with rivaroxaban exposure in subjects with normal renal function in the absence of erythromycin. Therefore, these preliminary findings suggest the possibility that a moderate CYP3A4 inhibitor (such as erythromycin) that by itself might increase rivaroxaban by only ~1.2 fold could result in a twofold or more increase in rivaroxaban exposure in subjects with mild to moderate renal impairment. Additional simulations (data not shown) suggested that altered plasma protein binding of rivaroxaban in patients with impaired renal function may also impact the prediction of the exposure change.

Conclusion: The FDA reviewers concluded that several mechanisms needed to be incorporated into the PBPK model in order to adequately evaluate the magnitude of *in vivo* drug–drug interactions in subjects with renal impairment. Furthermore, in their briefing document to the Cardiovascular and Renal Drugs Advisory Committee (19 March 2009), the FDA reviewers indicated that, in view of the notable dual pathway of elimination of rivaroxaban, "The potential effect of concurrent renal impairment and the use of a moderate/strong CYP3A4 inhibitor on rivaroxaban exposure is of particular concern, given [that] this interaction can result in an increased exposure greater than the sum of its parts, and this interaction was not evaluated or modeled by the applicant" (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM181524.pdf).

This analysis also supports the EMA's cautionary language regarding the potential for multiple impairments in its product information for rivaroxaban. This approach may also provide additional context for the regulatory question of whether a dedicated clinical study to quantify the PK and pharmacodynamic effects should be considered so that the dose may be optimized for this scenario.

Case 4. Specific regulatory questions: Can PBPK modeling and simulation indicate whether *in vivo* interaction studies are needed for a drug that is a CYP3A inhibitor *in vitro*? Can PBPK modeling and simulation indicate whether *in vivo* interaction and organ impairment studies are needed for a drug that is a CYP3A substrate?

Synopsis: Intended for intravenous infusion, cabazitaxel is predominantly metabolized *in vivo* by CYP3A isoenzymes (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000ClinPharmR.pdf). Cabazitaxel also inhibits CYP3A *in vitro* with an I/K_i ratio of > 0.1. The reviewers constructed a PBPK model for cabazitaxel on the basis of *in vitro* and *in vivo* metabolism data and *in vivo* PK parameters. The model was used to predict the outcome of the following scenarios that lacked *in vivo* data:

I. *In vivo* drug–drug interaction with a CYP3A substrate, midazolam
II. *In vivo* drug–drug interaction with a CYP3A inhibitor, ketoconazole
III. *In vivo* drug–drug interaction with a CYP3A inducer, rifampin
IV. PK of cabazitaxel in patients with various degrees of hepatic impairment

With this model, the simulated PK profile for cabazitaxel was comparable to the observed *in vivo* PK data. For scenario I, although I/K_i is > 0.1, the model predicted minimal drug–drug interactions when cabazitaxel and midazolam were coadministered, possibly because of the rapid disappearance of cabazitaxel in plasma during the distribution phase, its relatively high plasma protein binding, and the absence of inhibition of gut metabolism, as cabazitaxel is administered intravenously. The FDA reviewers also conducted a sensitivity analysis that incorporated a several-fold higher I/K_i ratio, in order to confirm the absence of CYP3A inhibition by cabazitaxel *in vivo* (Midazolam AUC ratio with and without inhibitor <1.1). For scenarios II and III, the PBPK model indicated that a drug–drug interaction was possible (i.e., the estimated ratio of cabazitaxel AUC with the inhibitor ketoconazole to that without was 2.2, and the corresponding ratio for the inducer rifampin was 0.6). For scenario IV, the PBPK model predicted higher increases in cabazitaxel exposure with higher degrees of hepatic impairment (the AUC is 2.5-fold higher in subjects with a Child-Pugh score of C as compared with healthy subjects).

Conclusion: The PBPK simulations indicate that an *in vivo* drug–drug interaction study with midazolam as a substrate is not required, even though cabazitaxel has an I/K_i > 0.1. The simulations confirmed the need to conduct *in vivo* drug–drug interaction studies with CYP3A inhibitor(s) and inducer(s). The simulations assisted the design of a PK study in hepatic impairment by supporting the use of a lower dose of cabazitaxel in patients with severe hepatic impairment in the planned hepatic impairment study.

DISCUSSION

The improvement in our understanding of human physiology and biochemistry, drug ADME, and mechanism of action; the availability of tools that allow us to model nonclinical and clinical pharmacology data; and the advancement of information technology have made it possible for us to utilize a systems-biology approach such as PBPK modeling to evaluate drug exposure changes due to individual patients' intrinsic and/or extrinsic factors (**Figure 1**). In this report, we present our regulatory experience in using PBPK modeling and simulations in addressing clinical pharmacology questions. The experience indicates that knowledge regarding both the system component and the drug-dependent component are essential in constructing an appropriate PBPK model.

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Table 3. Important parameters needed for comprehensive evaluation of complex drug interactions

Type of study	Parameters estimated
In vitro ADME and interaction	Enzyme/transporter involved in elimination and interaction Drug distribution (e.g., $f_{u,p}$ and B/P) Interaction mechanisms and parameters (e.g. K_i) Initial f_m estimation
Phase I dose escalation (oral administration)	CL/F_{oral} V/F_{oral} Likely f_e, CL_r and metabolite data
Absolute oral bioavailability	CL V Likely CL_r and metabolite data F_{oral}
In vivo mass balance (e.g., studies in humans using radiolabeled material)	Confirm f_m Confirm f_a Confirm f_e, CL_r

B/P, blood to plasma ratio; CL, clearance; CL_r, renal clearance; F_a, fraction absorbed; f_e, fraction of the dose excreted unchanged in the urine; F_{oral}, oral bioavailability; $f_{u,p}$, unbound fraction in plasma; K_i, reversible inhibition constant.; V, volume of distribution.

Modified from Zhao *et al.*[21]

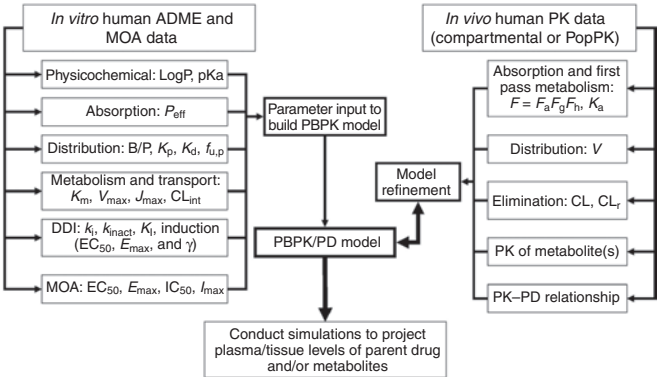

Figure 3 General scheme to incorporate drug-dependent parameters into a PBPK model. ADME, absorption, distribution, metabolism, and excretion (although "absorption" in this figure refers specifically to the passive processes of drug entry into systemic circulation, parameters such as jejunum permeability (P_{eff}), measurable *in vitro*, may be affected by active processes by transporters, and an array of factors influencing drug absorption have been reviewed by Jamei *et al.*[12]); AUC, area under the concentration-vs.-time curve; B/P, blood to plasma ratio; C_{max}, maximum concentration; CL, clearance; CL_{int}, intrinsic clearance; CL_r, renal clearance; DDI, drug–drug interactions; EC_{50} or IC_{50}, concentration causing half of the maximal effect of induction or inhibition; E_{max} or I_{max}, maximum effect of induction or inhibition; F, bioavailability; F_a, fraction absorbed; F_g, bioavailability in the gut; F_h, bioavailability in the liver; $f_{u,p}$, unbound fraction in plasma; γ, Hill coefficient; J_{max}, maximum rate of transporter-mediated efflux/uptake; K_a, first-order absorption rate constant; K_d, dissociation constant of drug–protein complex; K_i, reversible inhibition constant; K_I, apparent inactivation constant, concentration causing half of the maximal inactivation; k_{inact}, apparent maximum inactivation rate constant; K_m, Michaelis–Menten constant, substrate concentration causing half of the maximal reaction or transport; K_p, tissue-to-plasma partition coefficient; LogP, logarithm of the octanol–water partition coefficient; MOA, mechanism of action; PD, pharmacodynamics; P_{eff}, jejunum permeability; PK, pharmacokinetics; PopPK, population pharmacokinetics; V, volume of distribution; V_{max}, maximum rate of metabolite formation.

The four cases presented in this article describe the potential advantages of PBPK models over traditional models (e.g., compartmental models). PBPK models incorporate all available, relevant PK and physiology information, allowing the models to predict the effect of multiple factors on the drug concentration–time profile. The fact that these models are based on physiology helps scientists who are not clinical pharmacologists to understand the modeling results and incorporate them in drug development decisions. PBPK provides a more realistic prediction of the potential for drug–drug interactions than the static approach (such as the use of I/K_i) that has traditionally been used. The PBPK-based drug–drug interaction predictions are more realistic because they consider multiple factors and mechanisms that impact the interactions.[16–21]

As depicted in **Figure 2**, characterization and quantitative determination of elimination pathways of a drug and its metabolites is an important first step when conducting PBPK modeling and simulations. Based on our review of the submissions containing PBPK simulations, we noted that the lack of necessary information regarding clearance pathways has often hampered the proper use of the PBPK approaches. Without a thorough understanding of the ADME processes for an individual drug, it is difficult to quantify the effect of intrinsic and extrinsic factors on the PK of the drug. In order to appropriately characterize and quantify the contribution of specific enzymes and/or transporters to the overall disposition, several *in vitro* and *in vivo* studies appear to be indispensible under the current drug development paradigm (**Table 3**).

Figure 3 summarizes a general scheme to incorporate drug-dependent parameters into a PBPK model. Physicochemical parameters such as LogP, pKa, and polar surface area (experimentally determined or calculated based on chemical structure using *in silico* models) can be used to calculate tissue partitioning characteristics.[34–38] These parameters are also used when estimating microsomal protein binding and effective permeability that are not experimentally determined. *In vitro* metabolism and enzyme inhibition/induction parameters that are intended to describe drug clearance and drug–drug interaction mechanisms are experimentally determined and incorporated as input into PBPK models. A subsequent important step is the integration of *in vivo* knowledge to refine the PBPK model and to qualify the PBPK model by comparing the simulated PK profiles with those

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from available *in vivo* studies. For example, in order to carry out simultaneous evaluation of autoinhibition and multiple-dose effect on drug pharmacokinetics, one sponsor constructed the initial PBPK model using *in vitro* enzyme inhibition data and subsequently obtained PK parameters from phase 1 single-dose data to refine the enzyme kinetic parameters. Similar techniques were employed by reviewers when separately constructing PBPK models during the review process, using a variety of tools (see Methods).

During earlier stages of drug development, comprehensive drug-dependent parameters may not be available and the construction of a PBPK model relies largely on *in vitro* and *in silico* data. These initial models can be used to address certain regulatory questions in a qualitative manner as well as in candidate selection or optimization of clinical study designs. As the compound progresses to later stages of drug development, PBPK models could be iteratively refined to incorporate additional quantitative information on drug disposition from available *in vivo* studies. An adequately constructed PBPK model can play a critical role in designing clinical pharmacology studies by projecting drug PK profiles under various scenarios. It can also help in determining whether there is a need for additional studies, including postmarketing requirement or commitment studies, as part of risk–benefit assessment of new molecular entities.

This report focuses primarily on the utility of PBPK in assessing the mean drug exposure changes caused by intrinsic and/or extrinsic factors. Besides their deterministic features, population-based PBPK models can provide information related to variability and uncertainty of the PK profiles in patient subgroups.[39]

Despite the progress in the development of population-based PBPK modeling tools and their increased utility in pharmaceutical research, drug development, and regulatory review, quantitative prediction of certain clinical pharmacology scenarios is not possible because of several knowledge gaps. These gaps reside in both drug-independent (system-) and drug-dependent components. Like other modeling and simulation exercises, the use of PBPK is associated with various assumptions, which may vary depending on the stage of drug development and the regulatory questions to be addressed. One major knowledge gap is our insufficient understanding of developmental-related, disease-related, and organ dysfunction-related changes in human physiology. For example, knowledge regarding how renal impairment quantitatively affects the activities of individual metabolizing enzymes or transporters is critical in the construction of a PBPK model to assess the extent of drug interactions in patients with varying degrees of renal impairment. Similarly, we need an improved understanding of the effects of age on drug-metabolizing enzymes and transporters and renal function in both pediatric and geriatric populations. In addition, adequate characterization of the clearance pathways for drugs and their metabolites, and of the effects (induction and inhibition of specific enzymes and transporters) of interacting drugs is required. Besides the necessity to bridge these knowledge gaps, there is also a need for continued research to formulate and refine best practices in the use of PBPK approaches during drug development and regulatory review.[40,41] At the FDA, efforts have been undertaken to streamline the process of using PBPK during regulatory review, including criteria for conducting separate confirmatory PBPK modeling and simulations when reviewing PBPK data submitted by the sponsors.

In summary, between July 2008 and June 2010, the Office of Clinical Pharmacology at CDER, FDA, reviewed submissions for approval of INDs and NDAs that incorporated PBPK simulations. In this report, we summarize general schemes of PBPK simulation and propose procedures to obtain necessary data to construct PBPK models. In order to fully utilize PBPK in drug development and regulatory review, it is critical to adequately define mechanisms of drug disposition and understand general physiological perturbations related to diseases, age, and organ dysfunction.

METHODS

The Office of Clinical Pharmacology at the FDA has reviewed numerous submissions for approval of INDs and NDAs that included the use of PBPK modeling and simulations. Additional modeling and simulations were conducted by the FDA clinical pharmacology reviewers using a variety of software products. For example, when estimation of PK parameters using compartmental analysis was needed, mean concentration-vs.-time profiles (PK profiles) were digitized using GetData software (version 2.24, http://getdata-graph-digitizer.com). PK parameters were estimated by means of compartmental analyses using WinNonlin (version 5.2, Pharsight, Cary, NC). In other instances, PK of metabolites was considered important. Parameters for metabolites were obtained by fixing PK parameters of the parent drug in a model that incorporates metabolism. In one case, the values for volume of distribution, formation clearance, and elimination clearance of metabolites were estimated using NONMEM software or by manually adjusting the parameters in a PBPK simulator. PBPK simulators used in the submissions by sponsors and in the FDA reviews include Simcyp (Sheffield, UK), PK-Sim (Bayer Technologies, Leverkusen, Germany), and Gastroplus (Simulation Plus, Lancaster, CA). Other in-house PBPK models were developed using software such as SAAMII (University of Washington, Seattle, WA).

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Attachment 5.

R Madabushi, DS. Cox, M Hossain, DA. Boyle, BR. Patel, *et al.* **Pharmacokinetic and Pharmacodynamic Basis for Effective Argatroban Dosing in Pediatrics.** *J. Clin Pharamcol.* 51:19-28, 2011.

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Pharmacokinetic and Pharmacodynamic Basis for Effective Argatroban Dosing in Pediatrics

Rajanikanth Madabushi, PhD, Donna S. Cox, PhD, Mohammad Hossain, PhD, Duane A. Boyle, PharmD, Bela R. Patel, PhD, Guy Young, MD, Young-Moon Choi, PhD, and Jogarao V. S. Gobburu, PhD

The objective was to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of argatroban in pediatric patients and derive dosing recommendations. An open-label multicenter trial was conducted in pediatric patients (n = 18 from birth to 16 years). A population modeling approach was used to characterize pharmacokinetics and pharmacodynamics of argatroban in pediatric patients. Simulations were performed to derive a dosing regimen for pediatric patients. The estimated clearance of argatroban in pediatric patients was 2-fold lower than that in healthy adults. Body weight was significant predictor of argatroban clearance. The clearance in a typical 20-kg pediatric patient was 3.1 L/h. In 4 patients with elevated serum bilirubin levels, the estimated clearance was 0.6 L/h. Effect on activated plasma thromboplastin time (aPTT) was found to be concentration dependent. Simulations suggested that a starting dose of 0.75 μg/kg/min in pediatric patients was comparable in performance to 2.0 μg/kg/min approved in adults for attaining target aPTT and risk for bleeding. A dose increment step size of 0.25 μg/kg/min was suitable for titration. The PK/PD of argatroban was reasonably characterized in pediatrics. Plasma concentration–aPTT relationship was used to derive a safe starting dose and titration scheme for the first time in pediatric patients and was incorporated into the US prescribing information for argatroban.

Keywords: *Heparin-induced thrombocytopenia; argatroban; pediatrics; pharmacokinetics; pharmacodynamics; activated plasma thromboplastin time (aPTT); simulation*

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Argatroban, a synthetic thrombin inhibitor derived from L-arginine, has a selective inhibitory effect on the actions of thrombin, including fibrin formation and platelet aggregation. Argatroban injection (herein referred to as argatroban) is approved in the United States as an anticoagulant for prophylaxis or treatment of thrombosis in adult patients with heparin-induced thrombocytopenia (HIT) as well as in adult patients with or at risk for HIT undergoing percutaneous coronary intervention (PCI).

HIT is an immunological response that results in increased thrombin generation in response to heparin treatment. Usually HIT occurs between 5 and 14 days after initiation of heparin treatment, but it can occur more rapidly for those previously exposed to heparin.[1] The management of HIT, including HIT and thrombosis syndrome (HITTS), in adults consists of the immediate discontinuation of heparin and continued anticoagulation with alternative medications such as lepirudin or argatroban.[2,3] There are limited data on alternative anticoagulant therapy in children.[4] To date, there have been no well-controlled, randomized, clinical trials assessing alternative anticoagulant therapy in pediatric patients that have resulted in a change in clinical practice.[5] Accordingly, recommendations for anticoagulation in pediatric patients are usually extrapolated from dosing recommendations

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in adults. However, this approach is not ideal, because it does not account for the developmental changes that occur in the early days, months, and years of life that can profoundly affect responses to medications.[2,6] Hence, there is an unmet medical need for pediatric patients with HIT/HITTSS.

To encourage the pharmaceutical industry to conduct more studies in children, the US Congress added section 505A to the Food, Drug, and Cosmetic Act in 1997. Section 505A permits certain applications to obtain 6 months of additional market exclusivity (also known as pediatric exclusivity) if, in accordance with the requirements of the statute, the sponsor submits requested information relating to the use of the active moiety in the pediatric population.[7] The US Food and Drug Administration (FDA) issues a Written Request seeking submission of certain studies to determine whether the use of a drug could have meaningful health benefits in the pediatric population.

Encysive Pharmaceuticals along with GlaxoSmithKline submitted a pediatric efficacy supplement in response to a written request so as to obtain pediatric exclusivity. In the current article we report the dosing recommendations for argatroban in pediatric patients with HIT/HITTS derived from the data submitted to the argatroban supplemental new drug application. To our knowledge, the current article also reports for the first time the use of pharmacometric techniques for deriving the dosing recommendations for pediatrics in the area of hematology. Pharmacometrics is an emerging science designed to influence drug development and regulatory decisions by conducting quantitative analysis of dose/exposure (ie, pharmacokinetics [PK]), pharmacodynamics (PD) (eg, activated plasma thromboplastin time [aPTT]), and efficacy/safety data.[8-10]

METHODS

Patients

The study was a multicenter, open-label trial (NCT00039858 at ClinicalTrials.gov) conducted in pediatric patients (from birth through 16 years of age) from 1 of the 4 patient groups defined below[11]:

1. Patients with a clinical diagnosis of HIT or HITTS. HIT was defined as a decrease in platelet count to less than 100 000/μL or a 50% or greater decrease in platelet count after the initiation of heparin therapy with no apparent explanation other than HIT.
2. Patients who required anticoagulation and had a documented history of a positive HIT test in the absence of current thrombocytopenia (ie, patients at risk for HIT).
3. Patients who, in the opinion of the investigator, required alternative anticoagulation because of a suspicion of HIT (eg, a patient with previous heparin exposure in the absence of current platelet count or HIT antibody data).
4. Patients who, in the opinion of the investigator, required alternative anticoagulation because of an underlying condition, such as antithrombin III deficiency or heparin resistance.

Patient entry was stratified to ensure at least 8 patients in the youngest age group (birth to <6 months) and 8 patients in the oldest age group (8-16 years).

Dosing and Blood Sampling

Dosing recommendations in this study's protocol were based on the advice of physicians who had experience administering argatroban as an anticoagulant for different uses in pediatric patients. For patients who were undergoing procedures (ie, cardiac catheterization, cardiac surgery, ventricular assist device, extracorporeal membrane oxygenation, hemodialysis, or continuous veno-venous hemofiltration) and who required immediate systemic anticoagulation, an initial bolus of argatroban followed by a continuous infusion was recommended. A continuous infusion of argatroban without a bolus was also recommended for those patients with clinical conditions that required systemic anticoagulation. Once a patient was on a continuous intravenous infusion and had achieved a therapeutic aPTT or activated clotting time (ACT), the patient was to remain on this infusion dose until there was either clinical resolution of the underlying condition or discontinuation of argatroban for safety reasons or up to a maximum study period of 14 days, after which the investigator was permitted to continue therapy as needed, but off-study. Blood samples for analysis of argatroban concentrations (PK) were drawn throughout the treatment in conjunction with tests for aPTT or ACT (PD). All PK samples were obtained from a location that was separate from that of the infusion. Additional details regarding patient treatment, study assessments, and clinical outcome results are reported elsewhere.[11]

Analytical Assay

Argatroban was isolated from human plasma by protein precipitation and was quantified using

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turbo–ion spray interface liquid chromatography/tandem mass spectrometry (LC/MS/MS). Positive ion multiple reaction monitoring was used from the MS/MS detection of argatroban and the internal standard, nitrazepam. Based on 50 μL of plasma aliquot, the lower limit of quantification for argatroban was 5.00 ng/mL. Linear responses in analyte/internal standard peak area ratios were observed for analyte concentrations ranging from 5.00 to 1000 ng/mL. Intra-assay precision ranged from 5.84% to 7.96%. Interassay accuracy and precision ranged from 1.43% to 3.26% and 3.97% to 8.72%, respectively.

Data

Argatroban plasma concentration and aPTT/ACT data for concentration–aPTT (ie, PK/PD) model development and analyses were available from 5 studies in healthy adults (n = 52 subjects providing 1223 observations [PK = 600 and PD = 623]).[12-15] The doses studied ranged from 1 to 40 μg/kg/min with infusion durations ranging from 4 to 24 hours. In pediatric patients, evaluable argatroban plasma concentrations and aPTT/ACT were available from 15 patients. In these patients, a total of 167 plasma concentrations and 326 aPTT/ACT measurements were available. In 2 pediatric patients, ACT values instead of aPTT were measured. These ACT values were converted to aPTT values based on the established linear relationship between ACT and aPTT values in healthy volunteers.[12,13] The total duration of argatroban infusion in the pediatric patients ranged from less than 1 day up to 14 days, and the blood sampling schemes varied. The final PK/PD analysis used pooled adult and pediatric data consisting of a total of 1716 evaluable concentrations and aPTT observations from 67 subjects.

Data Analysis

Pharmacokinetic modeling. A population approach was adopted to characterize argatroban PK and the argatroban concentration–aPTT relationship in healthy adult subjects and pediatric patients using the NONMEM computer program (version V; (GloboMax, Hanover, Md).[16] Log-transformation of the concentration data was performed to reduce model instability and intensive computations. A 2-compartment open model was used to describe the concentration-time profile in healthy adults and pediatric patients. This model was parameterized in terms of plasma clearance (CL), volumes of distribution of the central compartment (V) and peripheral compartment (V_p), and intercompartmental clearance (CL_{ic}). Interindividual variability in model parameters was assumed to be log-normally distributed. An additive error model was used to account for the residual variability. A univariate forward selection approach was used to evaluate the impact of various predictors on argatroban pharmacokinetic parameters. The choice of the predictors was based on physiological plausibility and availability. The models were compared based on the objective function values, which are approximately the negative of twice the logarithm of the maximum likelihood of the data.[17] The difference in objective function value (DOFV) between any 2 nested models is approximately χ^2-distributed with n degrees of freedom, where n is the difference in the number of parameters between the 2 models. For example, a DOFV of 3.84 is significant at the 5% level and 10.83 at the 0.1% level, for 1 degree of freedom.[14] The comparison of hierarchical models was performed at the 0.1% level. Other criteria for model selection included goodness-of-fit plots, increases in precision of para-meter estimates, and reductions in interindividual and random residual variability. Continuous predictors (such as weight and age) were introduced in a linear fashion, whereas dichotomous predictors (such as gender or pediatric versus adult) were estimated using separate parameters or as a fractional change of the typical parameter.

Pharmacodynamic modeling. A sequential modeling approach was used to perform the concentration–aPTT analysis. A direct-effect simple E_{max} model was used to describe the concentration–aPTT relationship in healthy adults and pediatric patients. The model was parameterized in terms of the effect at baseline aPTT (E_0), the maximal increase in aPTT response from baseline (E_{max}), and the concentration of argatroban causing 50% of maximal response in aPTT (EC_{50}). Interindividual variability in model parameters was assumed to be log-normally distributed. A proportional error model was used to account for the random residual variability. The effect of various predictors on argatroban pharmacodynamics was evaluated in the same manner as described above for argatroban pharmacokinetics.

Simulations to derive optimal dosing. Simulations to explore the various dosing regimens were performed using SPLUS (version 7.0). A virtual population (consisting of 10 000 pediatric patients with normal hepatic function (HEP) and 10 000 adult subjects) was simulated from a uniform distribution of age from 0.042 (ie, 2 weeks) to 60 years.

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Table I Summary Statistics of Baseline Patient Demographics and Baseline Disease Characteristics

Characteristics	Birth to 6 mo (n = 8)	6 mo to <8 y (n = 6)	8 to 16 y (n = 4)
Age, y	0.29 (0.03-0.40)	5.07 (2.59-7.95)	13.38 (10.86-16.07)
Weight, kg	3.25 (2.60-6.00)	16.85 (13.00-23.00)	50.00 (30.80-108.00)
Height, cm	56.00 (39.00-65.00)	101.60 (91.00-115.00)	142.50 (130.00-174.00)
Gender, M/F	6/2	3/3	3/1
Baseline aPTT, s	36.30 (28.40-51.50)	39.30 (25.70-54.40)	37.7 (30.8-108.00)

aPTT, activated plasma thromboplastin time. The values in Table 1 represent: Mean (range)

The relationship between age and body weight for the simulations was modeled using the following equation developed from the current database:

$$Weight = 3.46kg + \left(\frac{88kg \bullet Age^{1.19}}{11yr + Age^{1.19}}\right) \bullet (1 + BSV)$$

where BSV = between-subject variability. The between-subject variability was assumed to be normally distributed with a mean of 0 and a coefficient of variation of 19%. The final relationship for population clearance of argatroban and the concentration–aPTT relationship was used to simulate steady-state argatroban plasma concentrations and the corresponding aPTT levels in these 10 000 pediatric patients. Various starting doses ranging from 0.25 to 3 µg/kg/min were simulated across pediatric patients in increments of 0.25 µg/kg/min. In addition, the adult approved starting dose of 2 µg/kg/min and the maximum approved dose of 10 µg/kg/min were simulated in 10 000 adult subjects to obtain predicted steady-state argatroban concentrations and aPTT levels.[18] A target aPTT of 1.5 to 3 times the baseline and not exceeding an aPTT value of 100 seconds was used as the target aPTT therapeutic window to compare the various starting doses in pediatric patients with the adult approved starting dose.[18] The percentage of patients within the target aPTT therapeutic window, above and below the targeted range, was computed for the various dosing regimens. To evaluate a titration strategy, patients with simulated aPTT values below the therapeutic window at a given starting dose were administered the next higher dose, and the percentage of these patients reaching the target aPTT window was calculated.

RESULTS

A total of 18 pediatric patients were screened and were enrolled in the study with the first enrollment in September 2003; the database was locked in January 2007. Summary statistics of baseline patient demographics stratified by age and baseline disease characteristics are depicted in Table I. At the time of enrollment, 8 patients had documented HIT, 2 patients were at risk for HIT, 5 patients were diagnosed with suspicion of HIT, and the remaining 3 patients required alternative anticoagulation because of an underlying condition, such as antithrombin III deficiency or heparin resistance.

Argatroban concentration–aPTT data were available for 16 patients. Data from 1 patient were not used for the pharmacokinetic analysis because only 2 argatroban plasma concentrations were obtained following a single bolus administration (15 minutes and 75 minutes post dose). These 2 plasma concentrations collected in the distribution phase did not provide adequate information to characterize the clearance in this patient. As a result, the observed argatroban concentration–time data for this patient were not well predicted and were treated as outliers and excluded from the analysis. Therefore, the argatroban concentration–aPTT modeling was conducted using data from only 15 pediatric patients. Four of these 15 patients had elevated serum total bilirubin (>2 mg/dL; range, 2.8-11.2 mg/dL) associated with hepatic impairment, secondary to cardiac complications resulting in hepatic congestion/poor perfusion (hereafter referred to as "hepatically impaired group"). One patient had elevated serum total bilirubin of approximately 3.2 mg/dL secondary to acute renal failure and therefore was not included in the hepatically impaired group.

Pharmacokinetic Modeling

A population PK model was developed to identify key prognostic factors that influenced the PK of argatroban in pediatric patients. A 2-compartment model was used to describe the PK of argatroban in both healthy

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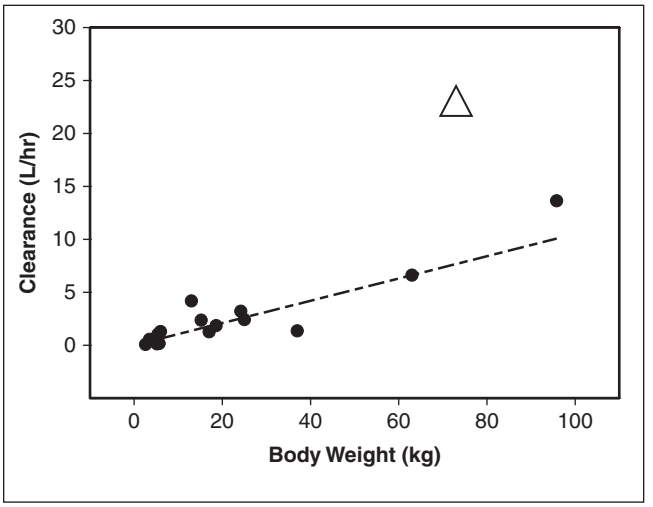

Figure 1. Clearance of argatroban in pediatric patients and healthy adults. The dots represent pediatric patients, the open triangle represents mean clearance in adults, and the dashed line represents weight-adjusted mean clearance.

adult subjects and pediatric patients. Results suggested that the clearance of argatroban was different in healthy adults and pediatric patients (Figure 1). Hence, argatroban clearance in adults and that in pediatric patients were estimated separately. Argatroban clearance was determined to be dependent upon patient's body weight, as seen in Figure 1. Introduction of body weight reduced the between-subject variability in clearance from 71% to 41% ($P < .001$). Age was not found to be a predictor of argatroban clearance in pediatric patients (Figure 2a). Furthermore, the hepatically impaired group exhibited lower clearance compared with pediatric patients with normal hepatic function after adjustment for body weight, as shown in Figure 2b. Adjustment of the clearance to account for elevated bilirubin status in pediatric patients further reduced the between-patient variability from 41% to 30% ($P < .001$). Body weight was also included as a predictor of other pharmacokinetic parameters (ie, V, V_p, and CL_{ic}) in the model. The diagnostic plots showing the goodness-of-fit for the final model are shown in Figure 3. The PK parameters along with their precision (percentage relative standard error) from the final PK model are shown in Table II.

Pharmacodynamic Modeling

A graphic assessment of argatroban concentration versus aPTT data showed that the effect on aPTT is dependent on plasma argatroban concentrations, as

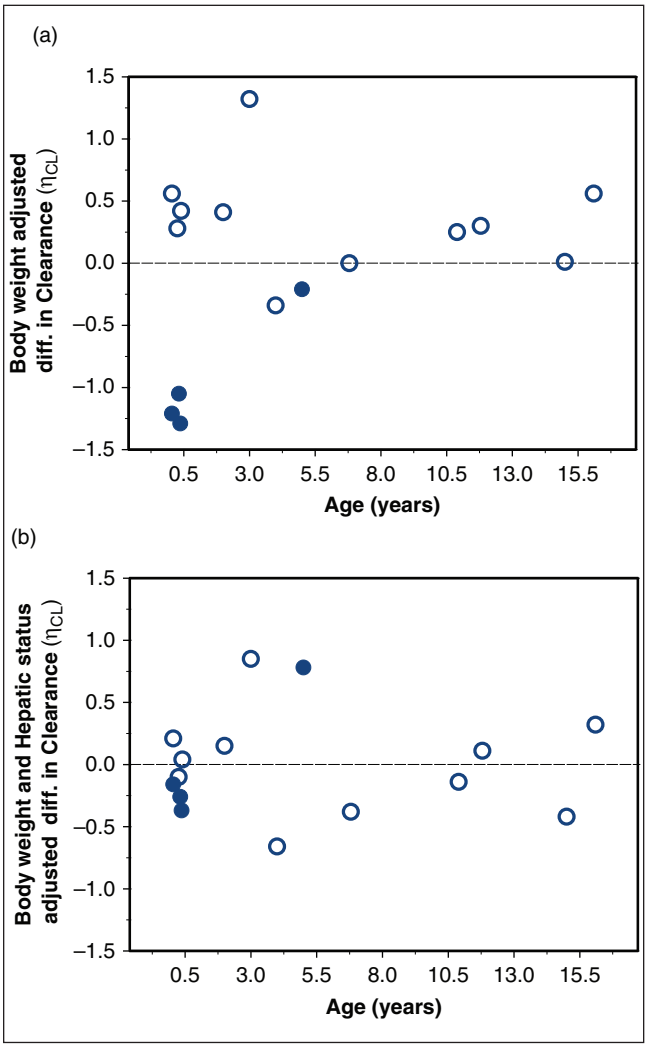

Figure 2. Effect of age and hepatic impairment on (a) weight-adjusted clearance and (b) weight and hepatic impairment–adjusted clearance of argatroban in pediatric patients. Open circles represent difference of individual clearance and adjusted mean clearance for pediatric patients with normal hepatic function, and closed circles represent pediatric patients with impaired hepatic function.

depicted in Figure 4. Furthermore, this relationship is similar between pediatric patients and healthy adults. A simple direct effect E_{max} model adequately described the argatroban concentration–aPTT relationship in healthy adults and pediatric patients. Covariate analysis did not reveal the effect of any predictors such as age, body weight, gender, and hepatic status on argatroban population concentration–aPTT parameters (ie, EC_{50}, E_{max}, or E_0). The diagnostic plots

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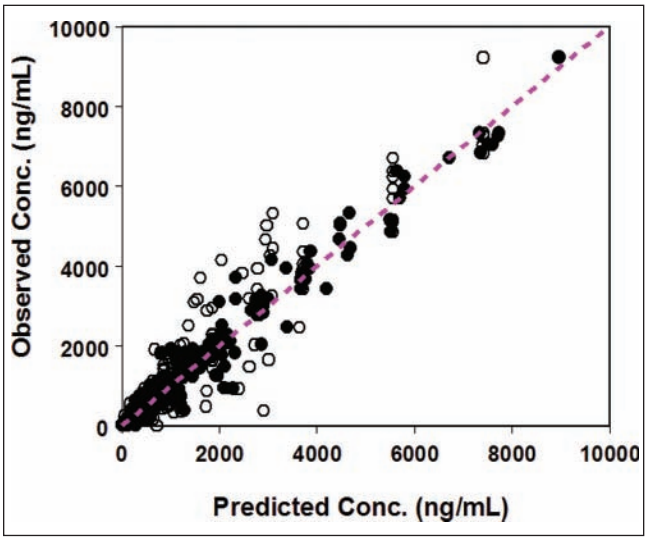

Figure 3. Goodness-of-fit plot for the final population pharmacokinetic model (covariates included). Open circles represent population predicted plasma concentrations, and closed circles represent individual predicted plasma concentrations of argatroban.

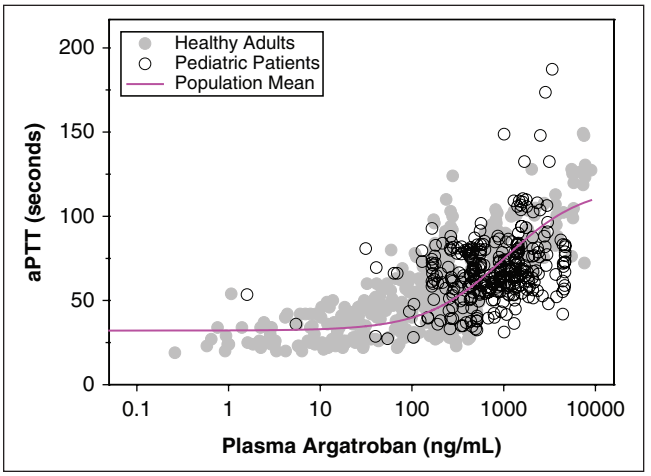

Figure 4. Argatroban plasma concentration–aPTT relationship in healthy adults and pediatric patients. Filled circles represent healthy adults, open circles represent pediatric patients, and the line is the model prediction.

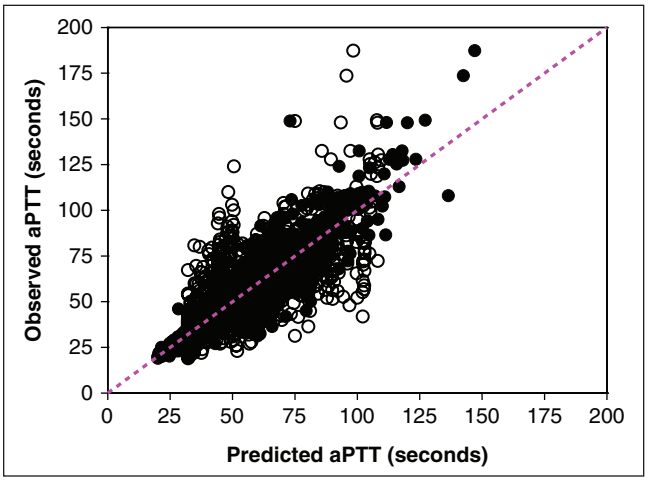

Figure 5. Goodness-of-fit plot for the pharmacokinetic/pharmacodynamic model for argatroban. Open circles represent the population predicted aPTT, and closed circles represent the individual predicted aPTT.

Table II Final Population Pharmacokinetic Parameters for Argatroban in Healthy Adults and Pediatric Patients

PK Parameter	Population Mean (%RSE)	Between-Subject Variability, %CV (%RSE)
CL, L/h/20 kg		29.7 (28.8)
Adult mean	6.3 (3.7)	
Pediatric mean	3.1 (15.6)	
Hepatic factor	–0.8 (9.8)	
V, L/20 kg	2.9 (9.6)	42.3 (29.1)
V_p, L/20 kg	1.6 (8.7)	19.4 (91.5)
CL_{ic}, L/h/20 kg	1.0 (18.5)	39.4 (64.5)
Residual error, %CV	33.5 (60.9)	NE

CL, plasma clearance; CL_{ic}, intercompartmental clearance; CV, coefficient of variation; NE, not estimated; PK, pharmacodynamic; RSE, relative standard error; V, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment.

$$CL_{Adult} = CL_{Adult\,Mean} \bullet \left(\frac{WT}{20}\right)$$

$$CL_{Ped} = CL_{Pediatrics\,Mean} \bullet \left(\frac{WT}{20}\right) \bullet \left(1 + \left(HEP_{Factor} \bullet HEP_{Status}\right)\right)$$

HEP_{Status}: 0 – Bilirubin <2 mg/dL
1 – Bilirubin >2 mg/dL

showing the goodness-of-fit for the final model are shown in Figure 5. The estimated concentration–aPTT parameters are shown in Table III.

Simulations to Derive Optimal Dosing

From a uniform distribution of age (0.042-60 years) and the body weight–age relationship, 10 000 pediatric patients and 10 000 adult subjects with normal hepatic function were simulated. Monte-Carlo simulations using the population PK model–derived body weight–clearance relationship and the between-subject variability in the pharmacokinetic parameters were performed to derive steady-state plasma

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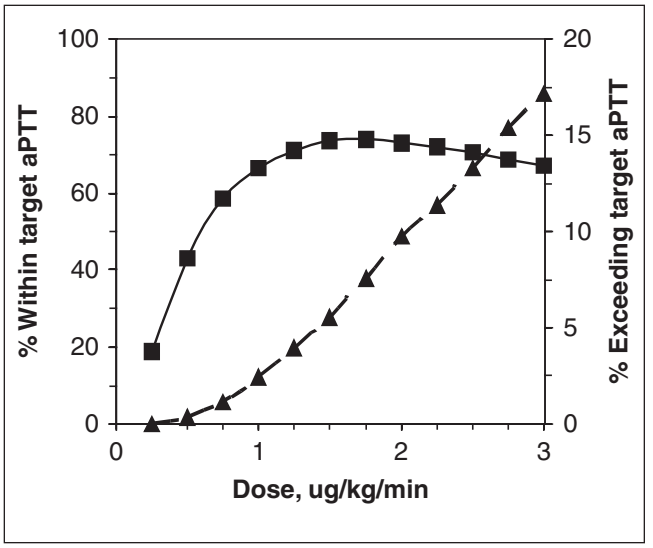

Figure 6. Percentage of patients within the target range (left y-axis) and percentage of patients at risk for bleeding (right y-axis) for each of the starting doses in pediatric patients. Squares represent patients within target; triangles represent patients at risk for bleeding. Target is defined as 1.5 to 3 times baseline aPTT and an absolute aPTT value less than 100 seconds.

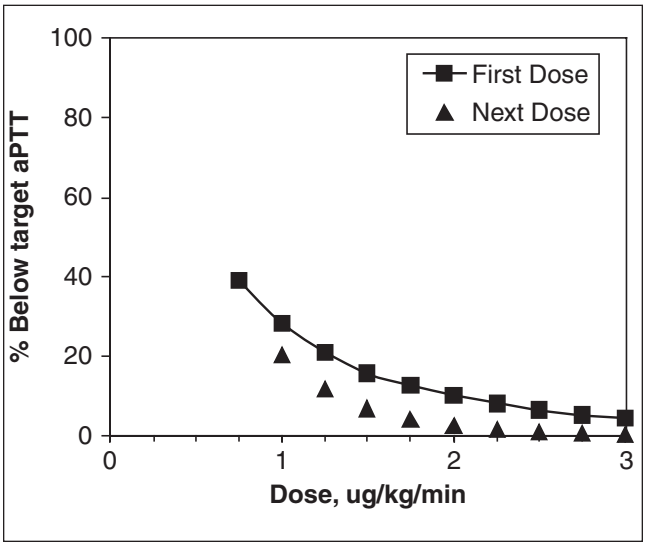

Figure 7. Comparison of fixed dosing and titration regimens. Squares represent the percentage of subjects below target aPTT with the fixed dosing regimen. Triangles represent the percentage of patients below target aPTT when the next higher dose was administered in increments of 0.25 µg/kg/min.

Table III Argatroban Population Concentration–aPTT Parameters for Healthy Adults and Pediatric Patients

Concentration–aPTT Parameter	Population Mean (%RSE)	Between-Subject Variability, %CV (%RSE)
E_0, s	31.8 (2.7)	20.9 (25.5)
E_{max}, s	84.4 (13.8)	25.3 (39.0)
EC_{50}, ng/mL	959.0 (22.5)	56.8 (31.7)
Residual error (%CV)	13.8 (12.9)	NE

aPTT, activated plasma thromboplastin time; C, argatroban plasma concentration; CV, coefficient of variation; E_0, effect at baseline aPTT; EC_{50}, concentration of argatroban causing 50% of maximal response in aPTT; E_{max}, maximal increase in aPTT response from baseline; NE, not estimated; RSE, relative standard error.

$$E = E0 + \left(\frac{E_{max} \bullet C}{EC_{50} + C}\right)$$

argatroban concentrations. The aPTT levels corresponding to the steady-state plasma concentrations were derived using the population concentration–aPTT relationship developed above for starting doses ranging from 0.25 to 3 µg/kg/min (in 0.25-µg/kg/min increments).

Increasing starting doses were associated with increasing percentages of patients being within the target aPTT therapeutic window up to starting doses of 1.25 µg/kg/min (Figure 6). However, the percentage of patients at potential risk for bleeding (ie, aPTT ratio >3.0) also increased linearly beyond a starting dose of 0.75 µg/kg/min, as shown in Figure 6. For comparison, in adults receiving the approved starting dose of 2 µg/kg/min, 67% patients were within the target therapeutic window and 2% patients were at potential risk for bleeding. With a starting dose of 0.75 µg/kg/min, approximately 39% of the patients did not reach the target aPTT window. Dosing these patients who did not reach the target aPTT therapeutic window with the next higher dose increased the percentage of patients falling within the target window, as shown in Figure 7. With a step size of 0.25 µg/kg/min, almost all patients reached the target aPTT therapeutic window with a maximum dose of 2 µg/kg/min.

DISCUSSION

The occurrence of HIT in heparinized pediatric patients is well documented, with an estimated incidence (1%-2%) comparable with that reported in

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adults.[19,20] HIT in children mainly occurs in the pediatric intensive care setting and has diagnostic features and outcomes similar to those seen in adults. Argatroban, an alternative anticoagulant that is structurally distinct from heparins, has been well characterized in adult patients with HIT/HITTS. However, no outcome trials for argatroban in pediatric patients have been conducted. Moreover, it is impractical to expect large prospective clinical trials in severely ill pediatric patients for orphan indications such as HIT/HITTS to enroll and complete successfully. The current study is an excellent example, taking 4 years to enroll and assessing only 18 pediatric patients from a total of 12 centers. In the absence of randomized studies, we are left with nonrandomized trials, case reports, and adult dosing recommendations to serve as critical data sources for supporting refinements to dosing guidance and facilitating medical decision making regarding anticoagulation in pediatric patients.[4,5] Hence, there is a need for systematic studies that provide useful dosing recommendations of argatroban to practicing pediatricians. Under these circumstances, it is imperative that the data generated in such studies be used to their fullest extent so as to provide meaningful dosing recommendations. It is also essential that the studies be planned in such a way that maximum information can be obtained. The success of the present analysis is a result of diligent data collection and efficient use of the data to arrive at dosing recommendations. In the present article we have presented an illustrative case for leveraging the exposure–response information from only 15 severely ill pediatric patients requiring nonheparin anticoagulation (eg, for HIT/HITTS), along with adult information, to derive dosing recommendations for thromboprophylaxis or treatment in the noninterventional setting. Use of innovative pharmacometric techniques enabled us to successfully derive individualized dosing recommendations.

Pharmacokinetics

The PK of argatroban has been extensively studied in adults, and a 2-compartment model has been found to describe the concentration-time profile. Hence, a 2-compartment PK model was used to describe healthy adult and pediatric patient data. In the present study, corresponding PK and PD data were available in 16 of 18 pediatric patients who were administered a median (range) infusion dose of 1.1 (0.3-13) μg/kg/min for a median (range) of 3.0 (0.1-13.8) days. Multiple steady-state plasma concentrations were available in the 15 pediatric patients that enabled reasonably precise estimation of argatroban clearance. Results depicted that the clearance of argatroban was approximately 2-fold lower in pediatric patients than in adults, consistent with that observed with the direct thrombin inhibitor lepirudin. The mean clearance of lepirudin in adult HIT patients (114 mL/min) was reported to be lower than in healthy adults (164 mL/min).[21] As expected, changes in body size lead to changes in clearance, and this relationship was consistent with allometric principles. An exponent of three-fourths[22] could not be adopted for the allometric relationship because the data were obtained from sick pediatric patients and healthy adult volunteers. The exponent of this allometric relationship was empirically estimated and was found to be 1.04. Hence, a linear relationship was adopted in the current analysis by fixing the power to 1. A similar linear relationship between body weight and clearance was reported previously for hepatically cleared drugs such as morphine.[23] Furthermore, for argatroban, body weight alone did not completely explain the between patient variability in pediatric patients. After accounting for the body weight, 3 of 6 patients younger than 6 months of age exhibited lower argatroban clearances. Age was not found to account for the systematic lower clearance as seen from the plots of age versus body weight–adjusted clearance plot (Figure 2a). Upon further exploration, these patients were found to have poor hepatic function as evidenced by elevated bilirubin levels secondary to cardiac complications resulting in hepatic congestion/poor perfusion. In pediatric patients administered argatroban, the hepatically impaired group was estimated to have 77% lower clearance compared with those with normal hepatic function in the final population PK model and also eliminated the systematic bias seen with body weight–adjusted clearance (Figure 2b). This finding is consistent with that seen in adults for argatroban, where patients with hepatic impairment have lower clearance and require one-fourth of the recommended starting dose.[18] Thus, with the available data not only were the pharmacokinetics of argatroban well characterized but the data were sufficient to describe the effect of hepatic impairment on argatroban clearance.

Pharmacodynamics

The argatroban–aPTT relationship was well characterized in pediatric patients because rich aPTT data

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were available over a wide concentration range, approximately 100 to 5000 ng/mL. The effect on aPTT is dependent on the argatroban plasma concentration (Figure 5). Furthermore, this relationship is similar between pediatrics and adults. This phenomenon is consistent with other anticoagulants such as heparin and molecular weight heparin.[24]

Simulations to Derive Optimal Dosing

The characterization of argatroban PK and concentration–aPTT relationship in pediatrics enabled us to use the PK/PD model to explore various dosing regimens for anticoagulation in the noninterventional setting. The goal of the simulation exercise was to derive a dosing regimen that would maximize the number of patients achieving the target aPTT therapeutic window. The exposure–response relationship was leveraged to perform simulations that compared the expected benefit (percentage of patients falling within the target aPTT therapeutic window) and risk (percentage of patients exceeding the target window and at an increased risk for bleeding) between various doses in pediatrics and in adults at the approved starting dose. Such a benefit–risk analysis allowed for successful derivation of a starting dose recommendation and titration scheme of argatroban in pediatric patients. In adults with a starting dose of 2 µg/kg/min, 67% patients would be predicted to attain the target aPTT, whereas 2% would exceed the target range and be at increased risk for bleeding. A starting dose of 0.75 µg/kg/min in pediatric patients results in a slightly lower percentage of patients (59%) reaching the target aPTT therapeutic window compared with adults. This starting dose in pediatrics was also associated with a lower percentage (1.2%) of patients exceeding the target window and being at increased risk for bleeding compared with the adult dose. The next higher step (ie, 1 µg/kg/min) resulted in a higher percentage of patients at risk for bleeding (2.4%). Because argatroban is titrated to effect, it is imperative that the starting dose be reasonably effective while still maintaining a lower risk for bleeding. Therefore, a starting dose of 0.75 µg/kg/min is reasonable in pediatric patients.

With this starting dose of 0.75 µg/kg/min, approximately 40% of pediatric patients would be predicted not to reach the target aPTT therapeutic window. To derive a dose titration strategy, further simulations using a step size of 0.25 µg/kg/min were conducted. For example, if 40% of the patients who had an aPTT ratio below the target after receiving the 0.75-µg/kg/min starting dose were administered the next higher dose (ie, 1 µg/kg/min), approximately 50% of these patients would achieve the target aPTT window. The remaining 50% of patients would be titrated to the next dose level (ie, 1.25 µg/kg/min) and if necessary would continue to receive higher doses in increments of 0.25 µg/kg/min. With this step size of 0.25 µg/kg/min, almost all patients would be predicted to reach the target aPTT window with a maximum dose of 2.0 µg/kg/min.

CONCLUSION

Conducting multiple trials investigating different combinations of starting doses and titration schemes in pediatrics, especially in HIT/HITTS patients, is impractical. Pharmacometric approaches can provide a powerful alternative to derive meaningful dosing recommendations.[25-28] The analysis presented in this article illustrates an example of efficiently using limited PK and PD data in pediatric patients along with data collected in adults to provide dosing recommendations for argatroban in pediatric patients in the noninterventional setting. Based on our analyses, the pediatric use section of the prescribing information for argatroban injection was updated to include recommendations for starting dose and titration strategy.[18] Additionally, dose adjustment recommendations for pediatric patients with hepatic impairment are provided.

The views expressed in this article are those of the authors and do not necessarily reflect the official views of FDA.

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