Executive summary

This white paper discusses the significant burden of diabetes in pediatric populations, including the limited treatment options for pediatric patients with type 2 diabetes mellitus (T2DM). While type 1 diabetes mellitus (T1DM) has historically been the predominant diabetes disease in pediatric populations, T2DM now accounts for more than 10% of the incident cases of diabetes between the ages of 12 and 16 years. Moreover, at 18 years of age the incidence of T1DM and T2DM is nearly identical.

Specific clinical, design, and operational considerations for pediatric clinical trials in this therapeutic area are addressed. These include rational study design and the realization that the protocol for a similar study in adults cannot be adapted merely by changing the age of eligible participants. Designing a protocol for a pediatric clinical trial requires an understanding of developmental physiology, emotional development, and the particular clinical and pathologic manifestations of the disease being studied. Careful attention must be paid to the specifics of the protocol as they pertain to pediatric participants (e.g., age-appropriate clinical endpoints, age-appropriate oral formulations that take into account developmental differences in taste ontogeny). Similarly, Principal Investigator and investigational site selection must consider suitability for and previous experience with pediatric clinical research.
Executive summary, continued

The relevant pediatric regulatory landscapes in the United States and Europe are reviewed. Discussions start with the origins of regulatory discourse focusing on the topic of drug development for pediatric populations, which began in earnest in the late 1990s, and progress to address regulatory considerations specific to diabetes therapies. While there are many similarities in what is required by EU and U.S. regulations, there are also notable differences that sponsors should be aware of when designing pediatric clinical programs.

Quintiles’ therapeutic expertise is leveraged within its Centers of Excellence (COEs). The specialized diabetes, pediatric, and regulatory expertise utilized during the preparation of this white paper was drawn from the Diabetes COE and the Pediatric COE.
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Introduction: The burden of pediatric diabetes

The burden of diabetes in children is significant. Incidence data from the SEARCH study confirms that T1DM is the major burden in patients less than 20 years of age. What is disturbing, however, is that T2DM now accounts for more than 10% of the incident cases of diabetes between 12 and 16 years of age, while at 18 years of age the incidence of T1DM and T2DM is nearly identical. In the past, T1DM was a disease of the young and T2DM a disease of adults. Now, T2DM has expanded to be the disease of older children.

Two treatment algorithms for the treatment of T2DM in youth are discussed here. The first was published in 2011 and was the result of consensus between the International Diabetes Federation (IDF) and the International Society for Pediatric and Adolescent Diabetes (ISPAD). The second was published in 2013 by the American Academy of Pediatrics (AAP). IDF identifies itself as the global advocate for people with diabetes, and its mission is to promote diabetes care, prevention and a cure worldwide. ISPAD is a professional organization whose aims are to promote clinical and basic science, research, education, and advocacy in childhood and adolescent diabetes. Their joint treatment algorithm is presented as Figure 1, and the list of recommended drugs is presented as Table 1.

Figure 1 2011 Global IDF/ISPAD guideline for diabetes in childhood and adolescence: Management of type 2 diabetes mellitus in childhood and adolescence

Reprinted with permission from the International Diabetes Foundation Guideline

* Blood glucose values < or > 130/180 (7.2/10 mmol/l) refer to self-monitoring of plasma blood glucose values of 90-130 mg/dl [5-7.2 mmol/l] fasting or preprandial and peak postprandial values of <180 mg/dl (10 mmol/l).
As with all treatment guidelines, the recommended therapies have risk/benefit data in the population for which they are indicated. What is surprising here is that no agent approved after 2000 is on this list, and that rosiglitazone is (still) a recommended therapy. At a joint meeting of FDA’s Endocrinologic and Metabolic Drugs Advisory Committee and its Drug Safety and Risk Management Advisory Committee convened in July 2010 to consider the cardiovascular safety of rosiglitazone, committee members voted on a list of predetermined, complex questions concerning potential regulatory actions. While 12 members voted in favor of removing rosiglitazone from the market due concerns over its cardiovascular safety, 20 members voted against such action. Of those 20, seven voted for additional warnings and 10 voted for additional warnings and restrictions on use of the drug. In concordance with these recommendations, FDA did not withdraw rosiglitazone from the U.S. market. However, the drug’s sponsor was required to submit a Risk Evaluation and Mitigation Strategy (REMS) within 60 days of the agency’s announcement of its decision on September 23, 2010. The required elements of the rosiglitazone REMS included:

- Provision of complete risk information to each patient, and documentation in his/her medical record that this information has been received and understood;
- Documentation from health care providers that each patient taking rosiglitazone falls into one of two groups:
  1. Patients currently taking rosiglitazone;
  2. Other individuals who are not able to achieve glycemic control on other medications, and who decide in consultation with their health care professional not to take pioglitazone (the other thiazolidinedione on the market) for medical reasons.
- Documentation from health care providers that the risk information has been shared with each patient;
- Physician, patient, and pharmacist enrollment.

Table 1 Drugs on IDF/ISPAD’s list

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>UK 1958</td>
</tr>
<tr>
<td></td>
<td>Canada 1972</td>
</tr>
<tr>
<td></td>
<td>U.S. 1995</td>
</tr>
<tr>
<td>SU (Glipizide)</td>
<td>1st 1984</td>
</tr>
<tr>
<td>Glargine</td>
<td>U.S. 2000</td>
</tr>
<tr>
<td>Meglitinide (Prandin)</td>
<td>U.S. 1997</td>
</tr>
<tr>
<td>Avandia (Rosiglitazone)</td>
<td>U.S. 1999</td>
</tr>
</tbody>
</table>

No agent approved after 2000 is on the IDF/ISPAD’s list of recommended therapies for T2DM in youth.
In contrast to the FDA's decision, and based on the same data and announced on the same day as the FDA's decision, the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use recommended the suspension of the marketing of rosiglitazone in European markets, and its marketing authorization remains suspended as of writing this paper. The EMA had no equivalent tool to the REMS that allowed the drug to stay approved (with heightened controls) in the United States. Despite the differences in form, the regulatory actions taken by the FDA and the EMA had similar practical consequences, and they have all but removed rosiglitazone as a treatment option for T2DM.

As noted previously, the AAP Guideline for management of newly diagnosed Type 2 diabetes mellitus in children and adolescents was published in 2013. Of note, the recommendation to initiate insulin therapy with HbA1c > 9% differs slightly from the ISPAD Guidelines. In general, high glucose in the absence of ketosis is treated in a stepwise manner with insulin as a last choice in the ISPAD Guidelines, while the AAP authors observe as follows: “Youth and adolescents who present with T2DM with poor glycemic control (BG concentrations ≥250 mg/dL or HbA1c >9%) but who lack evidence of ketosis or ketoacidosis may also benefit from initial treatment with insulin, at least on a short-term basis. This allows for quicker restoration of glycemic control and, theoretically, may allow islet β cells to “rest and recover.” Furthermore, it has been noted that initiation of insulin may increase long-term adherence to treatment in children and adolescents with T2DM by enhancing the patient’s perception of the seriousness of the disease. Many patients with T2DM can be weaned gradually from insulin therapy and subsequently managed with metformin.”

Key “action statements” included the following:

1. Clinicians must ensure that insulin therapy is initiated for children and adolescents with T2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between T1DM and T2DM is unclear. Additionally, in usual cases, should initiate insulin therapy for patients who have: (a) random venous or plasma blood glucose concentrations ≥250 mg/dL; or (b) an HbA1c reading >9%.

2. In all other instances, clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of T2DM.

3. The committee suggests that clinicians monitor HbA1c concentrations every three months and intensify treatment if treatment goals for finger-stick blood glucose and HbA1c concentrations are not being met.

4. The committee suggests that clinicians advise patients to monitor finger-stick blood glucose (see Key Action Statement 4 in the guideline for further details concentrations in patients who: (a) are taking insulin or other medications with a risk of hypoglycemia; (b) are initiating or changing their diabetes treatment regimen; (c) have not met treatment goals; or (d) have intercurrent illnesses.

5. The committee suggests that clinicians incorporate the Academy of Nutrition and Dietetics’ Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines in their dietary or nutrition counseling of patients with T2DM at the time of diagnosis and as part of ongoing management.

6. Clinicians should encourage children and adolescents with T2DM to engage in moderate-to-vigorous exercise for at least 60 minutes daily and to limit nonacademic “screen time” to less than two hours a day.

These treatment guidelines therefore demonstrate that there is a very large unmet need for innovative, safe therapies to treat T2DM in the pediatric population.
Regulatory landscapes for the prospective exclusion of unacceptable cardiovascular risk

Although the focus of this white paper is pediatric indication planning, which would be a label extension after an approval for treatment of adults with T2DM, it is beneficial to understand the requirements to demonstrate cardiovascular (CV) safety before approval for adult use would be granted. Both the FDA and EMA have now issued final guidance documents addressing the prospective exclusion of unacceptable cardiovascular risk for new antidiabetic drugs for T2DM. Quintiles has reviewed these documents and their intended and unintended consequences in detail in the peer-reviewed literature, and so only a brief summary of the fundamental tenets and intent are provided here.

The FDA guidance addressing this issue was issued in final format in December 2008. Cardiovascular risk is operationalized in terms of a relative risk ratio, with the number of Major Adverse Cardiovascular Events (MACE) composite endpoint events in the drug treatment group as the numerator and the number in the control group as the denominator; independent adjudication of all events is required. A meta-analysis involving MACE data from essentially all Phase II and Phase III trials is conducted, yielding a relative risk ratio point estimate. A two-sided 95% confidence interval (CI) is then placed around this point estimate, and the threshold of regulatory concern is defined as an upper CI limit of 1.8 or greater (see Turner for extended discussion of this statistical methodology).

Three scenarios are described in the guidance:

- If the upper limit of the CI is equal to or greater than 1.8, the drug would be deemed to have an unacceptable risk. In this case, “an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound before NDA/BLA (New Drug Application / Biologics License Application) submission.”

- If the upper bound is equal to or greater than 1.3 and also less than 1.8, and the overall risk-benefit analysis presented at submission supports marketing approval, “a postmarketing trial generally will be necessary to show definitively that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3.”

- If the upper limit is less than 1.3 and the overall risk-benefit analysis presented at submission supports marketing approval, “a postmarketing cardiovascular trial generally may not be necessary.”

The postmarketing cardiovascular trial referred to is a large-scale cardiovascular outcomes safety trial focusing on MACE outcomes (see Joffe et al.).

With two salient exceptions, the approaches in the FDA and EMA documents are comparable. The first one in the EMA document is that there are no explicit thresholds of regulatory concern corresponding to the values of 1.8 and 1.3 as presented in the FDA document with regard to a meta-analysis of data from Phase II and Phase III trials. The second is that the EMA wishes to be fully satisfied at the time of granting marketing approval that there are no unacceptable cardiovascular safety liabilities. Expressed in a slightly different manner, while not explicitly defining a statistical threshold, the EMA intends for sponsors to have prospectively excluded unacceptable cardiovascular risk to their (subjective) satisfaction by the time of submission. In contrast, the FDA accepts demonstration of a certain (explicitly specified) degree of cardiovascular safety at the time of submission, but in the vast majority of cases will require that a greater (and again specified) degree of cardiovascular safety be demonstrated as a post-approval commitment.

To satisfy either regulatory authority, in the vast majority of cases a large-scale cardiovascular outcomes safety trial will be needed, whether conducted pre- or post-approval. These studies are large, lengthy, and expensive: while each varies, meaningful figures are 5,000-15,000 participants, three to six years, and several hundreds of millions of U.S. dollars. An unintended consequence of the CV safety requirements may be that once a company makes the commitment to demonstrate CV safety in T2DM in adults, general safety, CV safety, and exposure data will be generated that far exceeds those recommended in ICH guidelines. If regulatory authorities were to accept these data as also satisfying the T1DM safety requirements, the T1DM development plan would only require efficacy studies (with concurrent safety
data measured). These efficacy studies may require fewer than 600 T1DM subjects. This is a very small incremental cost for a program initially designed to obtain an adult T2DM indication. If the risk/benefit in adults is deemed acceptable, appropriate studies in the pediatric T1DM population can be performed with another small incremental investment.

Considerations for successful pediatric clinical trials

Several considerations are of particular importance for the successful planning and execution of pediatric clinical trials. These include:

- Rational study design;
- Careful attention to specifics of the protocol as they pertain to pediatric participants; and
- Principal Investigator (PI) and investigational site considerations, including PI involvement, and recruitment and retention of not only participants but also their families.

Rational design

Pediatric protocol development is not merely a process of changing the age ranges employed in a similar adult trial, but requires thoughtful consideration with regard to pediatric-specific issues. Designing a protocol for a pediatric clinical trial requires an understanding of developmental physiology, emotional development, and the particular clinical and pathologic manifestations of the disease being studied. Often, while the particular disease process is similar between adults and pediatric patients, it is not identical. As such, specific endpoints applicable to adults may not be applicable to children. For example, many therapeutic agents being developed for the treatment of T2DM in adults evaluate secondary endpoints related to weight, with weight loss a desirable attribute. Because growth occurs in the pediatric age-range, changes in weight (and height) must be interpreted based on the “growth curve” for an individual participant, and absolute changes in weight as evaluated for adults may not be appropriate.

When recruiting for adult clinical trials one needs to look for participants with the disease or condition of clinical concern, and there may be a fair degree of latitude with regard to age. When recruiting for pediatric trials, however, the age of potential participants with the disease or condition of clinical concern becomes of particular importance and different pediatric age group may require different assents, modification of endpoint definitions, and use of age-appropriate laboratory norms. All of these factors are important in the development of an acceptable pediatric diabetes protocol.

Attention to protocol specifics

Specific protocol elements may also require a special approach when tailoring the design to include pediatric patients. One element concerns restrictions on the volume of blood draws, which impacts the number and timing of pharmacokinetic (PK) and/or lab samples. If such samples are to be taken, age-specific blood volumes must be considered. It is generally accepted that 3% of estimated circulating blood volume can be removed for study purposes over a two to eight-week period, but requirements are often governed by individual Institutional Review Boards (IRBs) and/or Ethics Committees.

Independent of the blood volume differences, various developmental factors must be considered when determining PK sample timing and analysis. These factors include expanded volume of distribution, which is maximal in infancy and decreases to adult numbers during late adolescence, and increased renal excretion, which changes as pediatric renal function changes across the age spectrum. Breast feeding versus formula feeding in newborns and infants is also relevant and will impact gastric emptying time.
Checking for nonsensical elements in the protocol is more important than one might intuitively suspect. For example, when recruiting very young children, questions concerning contraception, smoking, and alcoholic consumption habits are (hopefully) not needed. Laboratory and ECG monitoring require the use of appropriate pediatric norms which can vary significantly between the various age groups (infants v. adolescents). In general, most applicable pediatric programs should include the following:

- Informed consent and assent;
- Ethical considerations, including 21 Code of Federal Regulations (CFR) Part 50 definitions of risk;
- Safeguards for patient safety and monitoring, including rescue plans if appropriate;
- Good rationale for a placebo challenge or placebo arm if one is used;
- Therapeutically-specific endpoints that are also age-appropriate.

Additional points to note include the following:

- A sequential approach by age is often used, in which the older participants take part first, working down to the youngest, but this is dependent upon therapeutic area and available information in other populations. Rational study design;
- Information should be gathered that will be useful and not just nice-to-have; for example, pubertal evaluation (Tanner staging) should be performed as infrequently as possible, since this procedure may cause embarrassment to the participant, and lead to drop-out.
- In pediatric diabetes studies, age-appropriate blood glucose and HbA1c goals should be used. In addition, if the agent can increase the risk for hypoglycemia, the presence of (age-appropriate) hypoglycemic unawareness must be considered when preparing the protocol.
- Availability of an age-appropriate oral formulation must take into account developmental differences in taste ontogeny, including flavor and consistency.

**PI and site considerations**

Certain clinical trial considerations are specific to pediatric trials, and others that are always beneficial are particularly so in pediatric trials. The involvement and interest of the PI at each site is critical. In pediatric trials, it is the family that is “enrolled,” not just the participant.22 The sites therefore need to be both participant- and family-friendly, which includes the hours the site is open and the environment/facilities for both participant and family. The “culture” of the site must also be conducive to pediatric trial conduct, including a full understanding and implementation of consent and assent procedures and the ability and skill to discuss difficult issues such as positive urine drug tests. Also, site staff must also know how to address potentially sensitive issues such as birth control/sexual activity. Pediatric blood draws require special attention. A skilled pediatric phlebotomist comfortable with the use of topical anesthetics is required. Distraction techniques should also be considered at the time of any painful or stress-inducing procedure, and employed if appropriate. It is important that sites be familiar with looking for and minimizing distress because children are unable to articulate their experiences as well as adults.
Locating trial participants
Various characteristics of children and their diseases can lead to difficulties in locating sufficient participants for pediatric clinical trials: children tend to be healthy; when they have illnesses, these tend to acute; and, therefore, the proportion of children who have chronic illnesses is small. This necessitates that large safety/efficacy studies be global in nature, and requires careful consideration of several components of trial planning and execution:

• Regulatory landscapes, standard-of-care treatments, and sociocultural norms in each country (and in the case of the latter, regions within large countries) must be considered.
• Appropriate sites, PIs and institutions must be identified for each geographic region. This includes considering the availability of technology and equipment at candidate sites.

A key message is: Do not rely on adult diabetes mellitus drug development experience to be the sole driver of a pediatric strategy.

History and overview of pediatric regulations
Regulatory discourse focusing on the topic of drug development for pediatric populations began in earnest in the late 1990s, beginning in the United States with incentives provided for in the Food and Drug Modernization Act (FDAMA) of 1997, and followed quickly by the mandates included in the 1998 Pediatric Rule. FDAMA offered six months of additional marketing exclusivity or patent protection in exchange for conducting pediatric studies specified in an FDA-issued Written Request (this exclusivity provision was later reiterated as part of the Best Pharmaceuticals for Children Act of 2002).

The Pediatric Rule of 1998 mandated that for new products or indications under review, pediatric studies must be performed if the disease affects pediatric patients. The Pediatric Rule was enjoined in 2002 when a federal court ruled that FDA did not have the legislative authority to mandate the testing described in the Pediatric Rule. This led the following year to issuance of the Pediatric Research Equity Act (PREA), which provided the necessary authority and largely had the same requirements that had previously been part of the Pediatric Rule. PREA was reauthorized in 2007, the same year that similar regulations, collectively known as the Paediatric Regulation, came into force in the EU. Though pediatric regulations came into effect later in the EU than in the U.S., submission of a pediatric plan is generally required earlier in the EU, and follows a more prescriptive process. The European Commission has issued a guideline outlining in detail the content and format for the pediatric plan, which they have designated the Paediatric Investigational Plan (PIP).

Similarities and differences between EU and U.S. regulations
While there are many similarities in what is required by EU and U.S. regulations, there are also notable differences that sponsors should be aware of when designing their pediatric clinical programs: These are summarized in Table 2.
Table 2 U.S. and EU pediatric regulations: similarities and differences

<table>
<thead>
<tr>
<th>Submission</th>
<th>U.S. Pediatric Plan</th>
<th>EU Paediatric Investigation Plan (PIP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of pediatric/paediatric</td>
<td>Through 16 years old, inclusive</td>
<td>Through 17 years old, inclusive</td>
</tr>
<tr>
<td>Scope</td>
<td>New indication prior indications can be required for exclusivity</td>
<td>Prior and new indications</td>
</tr>
<tr>
<td>Waiver</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Deferral</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reward</td>
<td>6 month pediatric exclusivity if BPCA(^1) written request issued for the study</td>
<td>6 month Supplementary Protection Certificate</td>
</tr>
<tr>
<td>Submission timing</td>
<td>Within 60 days of EOP(^2) meeting(^3)</td>
<td>After the completion of adult PK</td>
</tr>
<tr>
<td>Approval timing</td>
<td>Prior to(^2) or with NDA/BLA approval</td>
<td>Required prior to MAA filing</td>
</tr>
<tr>
<td>Decision authority</td>
<td>Review Division</td>
<td>Paediatric Committee (PDCO)</td>
</tr>
<tr>
<td>Orphan drugs</td>
<td>Exempt from pediatric requirements</td>
<td>Not exempt, but eligible for additional 2 years exclusivity</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>Not exempt from pediatric requirements</td>
<td>Exempt from pediatric requirements</td>
</tr>
</tbody>
</table>

\(^1\) Best Pharmaceuticals for Children Act, 2002.
\(^2\) With the advent of the Food and Drug Administration Safety and Innovation Act (FDASIA), submission of the pediatric plan is to be within 60 days of EOP\(^2\) meeting, and approval within 210 days of submission.

Starting at the finish, an approved PIP is required in order to submit a Marketing Authorization Application in the EU, whereas the final pediatric plan must be agreed upon prior to approval of an NDA or BLA in the U.S. Given this difference, it has not been uncommon in the U.S. for sponsors to wait to delineate pediatric programs until quite late in the development program for the adult indication. However, with the passage of the FDA Safety and Innovation Act (FDASIA) of 2012, an initial pediatric plan is to be submitted within 60 days of an End of Phase 2 (EOP2) meeting, with approval of that plan targeted for within 210 days: 90 days for initial FDA review that culminates in FDA either meeting with or providing written comments to the sponsor; 90 days for sponsor agreement; and 30 days for FDA confirmation of the agreement. Submission of a pediatric plan shortly after EOP2 will narrow the gap with the EU’s request for submissions after the completion of adult PK studies. Though there is little experience to date with the new U.S. pediatric plan process mandated by FDASIA, it appears to be similar in overall timeframe with the EU PIP review process in which a two-month initial review is followed by a clock stop (typical length of approximately 3 months) during which the sponsor revises the PIP per the PDCO Request for Modification, and then by a two-month final review period that culminates in the adoption of the final PDCO Opinion.

It is worth noting that FDASIA makes the provisions of both PREA and BCPA permanent, such that they no longer require periodic reauthorization. FDASIA also mandates that the Pediatric Review Committee (PeRC) evaluate all pediatric plans, although the decision making authority remains with the therapeutic review division. In contrast, the Paediatric Committee (PDCO) has both review and decision-making authority in the EU.
Other differences between the EU and U.S. include how orphan drugs and biosimilars are affected by regulations in the two regions. In the U.S., orphan drugs are exempt from pediatric requirements. In the EU this is not the case; however, orphan drugs are eligible for an additional two years of pediatric exclusivity. For biosimilars the situation is somewhat reversed in that they are exempt from pediatric requirements in the EU, but not in the U.S. unless they are designated as interchangeable. Sponsors developing diabetes therapies that target early onset diabetes with residual beta cell function, an orphan indication, and certain insulin products that may qualify as biosimilars should be aware of the impact on their drug development programs of the regional regulatory differences.

In both the U.S. and EU, waivers and deferrals are granted for similar reasons. Waivers are granted if the drug is not expected to be safe or efficacious in children, if there are not a substantial number of pediatric patients with the disease, or if no significant benefit over existing therapies is anticipated. Notably, for the latter justification in the U.S., it is also necessary to demonstrate that the drug is not likely to be used in a substantial number of pediatric patients. Deferrals are fairly common because they are granted in several circumstances: when it is appropriate to conduct studies in adults first; when studies in children will take longer; and when additional time is needed to develop pediatric formulations. It should be made clear here that deferral refers to implementation of the pediatric plan, not submission and approval of the plan, so it remains necessary to include pediatric planning early in a drug development program.

**Return on investment for the sponsor**

Generation of data to provide better information regarding the use of drugs to treat children can often provide direct benefit to the sponsor. While both the U.S. and EU offer six-month extensions of exclusivity, in the U.S. exclusivity is granted only if the studies are the subject of an FDA Written Request, which necessitates a process that is separate from the approval of the pediatric plan. Whereas the studies that can be required per PREA are limited to the new indication being sought in adults, BCPA Written Requests can encompass additional indications, including those previously approved and/or those not in the label, if FDA believes this information will improve use of the drug in children. In the EU, although the granting of exclusivity is more directly linked to the PIP process, all indications in the label, both those previously approved and the new indication, are expected to be addressed in the PIP. In the EU, there is also a special marketing application for off-patent drugs developed for pediatric use called the Pediatric Use Marketing Application (PUMA) that results in 10 years of exclusivity.

Even with the substantial investment that can be associated with pediatric development, with the cost of a PK study averaging U.S.$900,000 and safety and efficacy studies ranging from U.S.$2-13 million, the financial return generally exceeds the investment. The return on investment associated with the extension of exclusivity was recently estimated to be as high as $73 for each dollar invested, with the diabetes drug that was included in the analysis cohort returning $22 dollars per dollar. Related information is provided in Table 3.
As noted earlier, it is possible in the EU to request a waiver based on there being no significant benefit of the drug over existing treatments for pediatric patients. However, given the potential financial return, it is not necessarily in the sponsor’s best interest to do so. Furthermore, the negative commercial implications if that argument, which is a matter of public record, is extended to the adult indication by competitors must be considered. Having no pediatric information in the labeling could also be a competitive disadvantage if other drugs for the indication do have such labeling. Finally, pediatric studies will still be required to access the U.S. market unless the drug is not likely to be used in a substantial number of pediatric patients.

Regulatory considerations specific to diabetes therapies

During the period of time when pediatric regulations were being promulgated, the International Conference on Harmonisation (ICH) issued the E11 Guidance: Clinical Investigation of Medicinal Products in the Pediatric Population, which embodied the general considerations for pediatric drug development and came into effect in January 2001. In 2002, EMA issued guidance for development of diabetes therapies, and a revision of the document was issued in 2012. FDA issued draft guidance for development of diabetes therapies in 2008. Both the EMA and FDA documents include information on issues specific to clinical development in the pediatric patient population.

ICH E11 opens with a list of general considerations for pediatric drug development that range from assessing the prevalence of the disease in children to consideration of whether pediatric-specific trial endpoints or drug formulations will be necessary. For diabetes, the pediatric prevalence of T1DM warrants the study of children of very young ages (study of the drug in children as young as one year of age was included in the 2010 PIP for insulin detemir), whereas the demographics of T2DM is such that studies in children 10 years of age or older are recommended. While HbA1c is well established as a primary efficacy endpoint for both adult and pediatric diabetes trials, additional safety endpoints to assess growth, pubertal development, bone development and neurocognitive development may be warranted for pediatric trials. There is also heightened concern regarding the effects of hypoglycemia in pediatric patients because of the potential for central nervous system (CNS) complications associated with severe episodes. It is understood that children are more prone to hypoglycemic episodes, but a drug should not increase the risk relative to alternative treatments. With regard to drug formulation, parenteral drugs to treat T1DM diabetes do not generally require reformulation for pediatric use: however, non-parenteral drugs would require formulations appropriate for young children to be developed. Reformulation has not generally been necessary for T2DM therapies, but sponsors have been asked to include an assessment children’s ability to swallow large tablet dosage forms in clinical trials.

Table 3 Return on investment for pediatric trials

<table>
<thead>
<tr>
<th>Indication</th>
<th>Net benefit ($M)</th>
<th>Net return-to-cost ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>$41</td>
<td>3.95</td>
</tr>
<tr>
<td>Asthma/allergy</td>
<td>$178</td>
<td>12.44</td>
</tr>
<tr>
<td>Osteogenesis</td>
<td>$208</td>
<td>26.85</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>($9)</td>
<td>-0.68</td>
</tr>
<tr>
<td>GI reflux</td>
<td>$507</td>
<td>73.63</td>
</tr>
<tr>
<td>T2 diabetes</td>
<td>$134</td>
<td>21.72</td>
</tr>
<tr>
<td>ADHD</td>
<td>$69</td>
<td>2.31</td>
</tr>
<tr>
<td>Refractory tumors</td>
<td>$119</td>
<td>32.25</td>
</tr>
<tr>
<td>Depression/general anxiety disorder</td>
<td>$242</td>
<td>6.98</td>
</tr>
</tbody>
</table>

Source: Information obtained from Li et al.

For diabetes, the pediatric prevalence of T1DM warrants the study of children of very young ages, whereas the demographics of T2DM is such that studies in children 10 years of age or older are recommended.
As mentioned previously, deferral of pediatric studies is fairly common in order to accumulate experience in adults that allows a benefit-risk assessment prior to studies in children. This sentiment is expressed in the 2008 FDA diabetes draft guidance by the statement that early studies of new drug classes should be limited to adults until “metabolism, pharmacodynamics and safety … are reasonably well defined.” In practice, this has translated into pediatric studies of T2DM therapies being initiated after approval for treatment of adults. T2DM pediatric programs generally start with a PK study that is followed by a short-term 12-week efficacy study and an extension phase to provide 12 months of exposure, the latter being stipulated in the EMA guidance and also consistent with recent PREA-mandated studies. Because a large proportion of T1DM patients are children, pediatric patients are generally included earlier in clinical trials, with the FDA guidance recommending that study of a drug in pediatric patients be prior to approval unless there are potential safety concerns or uncertainties such as those with inhaled insulins. For non-insulin T1DM drugs, the EMA guidance recommends a step-down approach, collecting safety and efficacy data in older age groups prior to studying younger age groups, and though it is not specified in the draft FDA guidance, it can reasonably be assumed that FDA likewise advocates this approach. For insulin drugs, the EMA guidance stipulates that pediatric patients should be stratified by age group (less than one year old, one to less than six years old, six to less than 12 years old, and 12 to less than 18 years old). One advantage of this stratification is improvement in the ability to interpret hypoglycemia results since susceptibility to hypoglycemia varies with age.

Based on information in the guidances and the experience with diabetes drug development in recent years, an outline of a typical pediatric clinical program can be described, although the timing of the studies and the ability to enroll pediatric participants in initial licensing trials compared with trials performed after approval of the adult indication differ for T1DM and T2DM therapies, as described previously. If a product requires a new formulation for pediatric use, the first study is not in pediatric participants: it is a bioavailability comparison in adults of the adult and pediatric formulations. The clinical program then progresses to a doseranging PK study in pediatric participants, with a single administration of drug being sufficient if PK is linear in adults. The results of the PK study then inform dose selection for the short-term efficacy (e.g., 12-week HbA1c) and long-term safety evaluations. The latter are generally 12 months, although longer periods may be warranted depending on the mechanism of action of the drug. For drugs that seek indications of both T1DM and T2DM, there may be an opportunity to leverage the long-term safety data collected for the first indication when designing the clinical program for the second indication. Based on recent PDCO decisions, PREA requests, and clinical trials that have been performed, the typical trial size for T2DM is 220–240 participants. For T1DM, a recent study was nearly in the same size range, with 265 participants aged between six and 16 years old and 82 participants aged between two and five years old.

Whether juvenile animal studies are needed prior to pediatric clinical studies varies from case to case, presumably depending on data from the standard nonclinical studies as well as clinical data collected in adults. For certain classes of drugs additional types of nonclinical studies have been requested, e.g., studies to evaluate comparative thyroid toxicity for glucagon-like peptide-1 (GLP-1) agonists. The GLP-1 receptor, however, is less highly expressed on C-cells in humans than rodents, complicating data interpretation.

Developing a pediatric plan

When preparing a pediatric development program, it is critical that the program be designed to address global regulatory requirements. The most specific and defined pediatric regulations are those in the U.S. and EU. The requirements are many, and the program typically will be multiphase, proceeding from studies on bioavailability of pediatric formulations, when needed, to PK studies and then efficacy and long-term safety studies. There are some differences between the U.S. and EU regulations and processes for which sponsors should plan prospectively. Although the resources required for pediatric development are not insignificant, the return on investment is generally positive. Likely the most important advice that can be given is to prepare a pediatric plan early in development, keeping in mind that creating and executing the plan can have very different timelines. By having a well-developed plan in place early in development, pediatric requirements need not delay market entry of a drug.
Concluding comments

There is a large unmet need for new therapies in the pediatric diabetes patient population: the disease burden is high, involving both T1DM and T2DM, and there are limited treatment options. This white paper has discussed a wide range of issues, and several points should be borne in mind when conducting pediatric trials in this therapeutic area:

- FDA and EMA pediatric regulations should be considered early in clinical development discussions;
- Pediatric requirements need not delay market entry of the drug for the adult population, provided that you have a well-constructed pediatric plan;
- There are benefits to doing pediatric studies, including extension of marketing exclusivity;
- Knowledge of the specific pediatric patient population from which clinical trial participants will be enrolled is important;
- Site and PI selection, study design, and protocol development need be done with a pediatric focus to achieve success.
References


10. Sutter S, Davis J. FDA, EMA decisions on Avandia reflect the power of REMS. “The Pink Sheet:” Prescription Pharmaceuticals and Biotechnology. 2010; September 27th, 1 and 4-6.


References, continued


23. The previous version of the Pediatric Rule, issued in 1994, was far less effective in generating data in pediatric patients. It focused on allowing labeling that extrapolated adult efficacy data to pediatric patients if it could be concluded that the course of the disease and effects of the drug were sufficiently similar in adults and children, and there was information supporting pediatric use.


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Robin provides strategic drug development advice to customers and internal teams, helping to shape clinical development programs that maximize value for both patients and drug manufacturers. She develops global regulatory strategies that consider commercial implications and minimize timelines, while maintaining a high likelihood of regulatory acceptance. As a member of the Pediatric Center of Excellence, she provides oversight of the comprehensive drug development process across a variety of indications with a focus on pediatric use of medicines. Robin specializes in applying regulatory expertise to clinical trial design, developing worldwide regulatory strategies, and negotiating with global regulatory authorities including FDA, EMA and national authorities.

Robin earned a PhD in Pharmacology from Duke University as a Howard Hughes Medical Institute Fellow. Prior to joining Quintiles in 2012, she served as Head of Regulatory Coordination at Grifols Therapeutics and its predecessor, Talecris Biotherapeutics, where she established worldwide regulatory strategies and negotiated with global regulatory authorities to expedite acceptance of clinical development programs. Robin began her career as a regulatory reviewer and then supervisor for the FDA’s Center for Drug Evaluation and Research.

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