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Summary of the NICHD-BPCA Pediatric Formulation Initiatives Workshop-Pediatric Biopharmaceutics Classification System (PBCS) Working Group

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Abstract

The Biopharmaceutics Classification System (BCS) allows compounds to be classified based on their *in vitro* solubility and intestinal permeability. The BCS has found widespread use in the pharmaceutical community as an enabling guide for the rational selection of compounds, formulation for clinical advancement and generic biowaivers. The Pediatric Biopharmaceutics Classification System (PBCS) working group was convened to consider the possibility of developing an analogous pediatric based classification system. Since there are distinct developmental differences that can alter intestinal contents, volumes, permeability and potentially biorelevant solubilities at the different ages, the PBCS working group focused on identifying age specific issues that would need to be considered in establishing a flexible, yet rigorous PBCS.

Objective—To summarize the findings of the PBCS working group and provide insights into considerations required for the development of a pediatric based biopharmaceutics classification system.

Methods—Through several meetings conducted both at The Eunice Kennedy Shriver National Institute of Child Health, Human Development (NICHD)-US Pediatric Formulation Initiative (PFI) workshop (November 2011) and via teleconferences, the PBCS working group considered several high level questions that were raised to frame the classification system. In addition, the

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PBCS working group identified a number of knowledge gaps that would need to be addressed in order to develop a rigorous PBCS.

Results—It was determined that for a PBCS to be truly meaningful, it would need to be broken down into several different age groups that would account for developmental changes in intestinal permeability, luminal contents, and gastrointestinal transit. Several critical knowledge gaps where identified including: 1) a lack of fully understanding the ontogeny of drug metabolizing enzymes and transporters along the gastrointestinal (GI) tract, in the liver and in the kidney; 2) an incomplete understanding of age-based changes in the GI, liver and kidney physiology; 3) a clear need to better understand age-based intestinal permeability and fraction absorbed required to develop the PBCS; 4) a clear need for the development and organization of pediatric tissue biobanks to serve as a source for ontogenic research; and 5) a lack of literature published in age-based pediatric pharmacokinetics in order to build Physiologically- and Population-Based Pharmacokinetic (PBPK) databases.

Conclusions—To begin the process of establishing a PBPK model, ten pediatric therapeutic agents were selected (based on their adult BCS classifications). Those agents should be targeted for additional research in the future. The PBCS working group also identified several areas where a greater emphasis on research is needed to enable the development of a PBCS.

INTRODUCTION

Developmental changes from birth through adolescence lead to a significant amount of variability in the Absorption, Distribution, Metabolism and Excretion (ADME) of therapeutic agents from birth to adolescence that are poorly understood.[1,2,3] Incomplete knowledge of the physiological changes that occur along the gastrointestinal tract and in the liver in response to growth and maturation further hinder our ability to accurately predict the *in vivo* pharmacokinetic and pharmacodynamic (PK/PD) behavior of novel and traditional pediatric medicines.

Based on these challenges, regulatory agencies including the FDA and the EU have taken significant steps towards incentivizing the pharmaceutical industry to devote more resources to research in this area.[4] These incentives (e.g., six months of added exclusivity) were included in the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) falling under the FDA Amendments Act of 2007 (FDAAA) and have helped lead to some advances by the pharmaceutical industry in developing pediatric formulations.[4,5] Furthermore, the public funding agencies have also provided additional support for pediatric drug discovery and clinical testing.[6] Despite these advances and incentives, there are still considerable risks and concerns regarding pediatric drug development (e.g. extemporaneous compounding).[7,8] These factors have contributed to the fact that children largely remain “therapeutic orphans” fifty years after Dr. Harry Shirkey first labeled them as such.[9]

In order to further promote informed pediatric formulation development, the PBCS working group was charged with the task of developing an age based classification system that would aid investigators in establishing formulations (particularly oral) of traditional and novel therapeutic agents for children. We focused on the Biopharmaceutics Classification System (BCS), which has gained broad acceptance in the pharmaceutical industry and has significantly impacted drug development. The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability.[10–12] Furthermore, the BCS takes into account three major factors that govern the rate and extent of drug absorption from immediate-release solid oral dosage forms: solubility, permeability, and dissolution. Briefly, the BCS is divided into four classes:

1. Class 1 drugs have both high solubility and permeability;

2. Class 2 drugs have low solubility and high permeability;
3. Class 3 drugs have high solubility and low permeability;
4. Class 4 drugs have both low solubility and permeability.

There are several factors that can significantly influence the BCS classification including; drug product composition, the physical properties of the drug substance (e.g, amorphous vs. crystalline), gastric emptying rates, gastrointestinal (GI) volume and flow rates and intestinal segment residence times; further the effect of the drug on GI motility; the variable chemical constitution of the intestinal milieu; and the affects of disease states on the pathophysiology of the GI tract need to be considered.[11–16] Drug development strategies and excipient selection can also be affected by the BCS classification of the agent.[16] For example, some poorly soluble compounds can be subjected to solubilization methods used in formulation development including salt formation, complexation, surfactants, co-solvents, nanosizing or micronizing, and the formation of amorphous or high-energy states that can alter apparent solubility and dissolution, and potentially significantly affect the drug's initial rate and extent of intestinal absorption.[13,15,16]

While the BCS has broad applicability, it was developed for adult formulations and is often more reliable when the intestinal permeability data has been established *in vivo* as compared to *in vitro*. Since pediatric growth and development is associated with ontogenic physiological changes in the GI tract, it was clear to the committee that it is essential to consider the impact of these changes on pediatric intestinal absorption. Furthermore, *in vivo* solubilities are expected to be different from those in adult population based on changes in the pediatric GI fluid compositions especially those that occur over time with development.

The expression of transporters and drug metabolizing enzymes which influence oral systemic availability from GI tract and vary during development must be considered. Another system that may be useful is the Biopharmaceutics Drug Disposition Classification System (BDDCS), which also characterizes drugs based on solubility and fraction dose metabolized.[17–19] The BDDCS while based in part on the BCS, is based on a drug's metabolism, specifically fraction dose metabolized, rather than intestinal permeability. The BDDCS provides an approach that may be more applicable to classifying new chemical entities found in early discovery stages based on preclinical data.[19] The BDDCS is based on the observation that BCS Class I and II compounds are largely eliminated by metabolism, while BCS Class III and IV compounds are largely eliminated by renal or biliary excretion. This generalization seems to be largely true and BCS and BDDCS classifications are largely congruent. Compounds for which the classifications are not in agreement need to be examined carefully. This is case for compounds that are transported by carrier mediated processes in/on the intestinal epithelial cell (absorbed and exorbed or secreted) or have pH dependent solubility and segment (position) dependent permeability along the GI tract. Based on the desire to integrate these areas, the PBCS working group considered the information that is currently available in addition to critical knowledge gaps that would need to be addressed in order to develop a Pediatric Biopharmaceutics Classification System (PBCS) for age based populations of children. The summary of these discussions are presented below.

AGE CLASSIFICATIONS

Pediatric patients represent a changing and dynamic population when considering classification system due to the ontogenic changes that occur during development. In order to properly classify drugs for pediatric utilization, age-dependent changes in the gastrointestinal physiology and biochemistry (e.g. transporters and enzymes) need to be determined and it is likely to be more appropriate to develop several age (or a more

appropriate GI developmental) specific criteria. A Pediatric Biopharmaceutics Classification Systems that properly accounts for the physiological changes that affect drug absorption and disposition, as well as safety, is needed. As a starting point, it was concluded that the selected age ranges could be divided into six groups that we would closely evaluate followed through adolescents: 1) Neonates (≤ 40 weeks post conception); 2) Infants (0–6 months old); 3) Infants (6–12 months old); 4) Toddlers (1–3 years old); 5) Children (4–6 years old); 6) Children (7–12 years old); and 7) adolescents (13–18 years old). While it has been suggested that six age groups are appropriate,[8] it was felt that for a more comprehensive evaluation to determine age-based effects, seven (or more) categories might be more physiologically meaningful. Reclassification of these age groups could be performed when developing the PBCS, which will be predicated on an exhaustive literature review as well as new research evidence focused on oral dosage form development for these pediatric groups.

AGE BASED CHANGES IN GASTROINTESTINAL PHYSIOLOGY

An extensive discussion occurred regarding the developmental effects on the GI and liver physiology in the seven proposed age groups. For the purpose of developing a PBCS model, we decided to focus on the GI physiology with intestinal permeability being the main driver for classification. The GI fluid composition, pH, and volume differences at each age group were identified as being critical for the development of the PBCS since these will influence age-based biorelevant solubilities and dissolution rates from formulations. It was concluded that there is some information available regarding fluid composition and pH, although the age at which they reflect adult values remains unclear.

Intestinal volumes have also been described, but there are differences between functional volume and volume capacity. For example, it has been established the neonatal and birth gastric pH values are close to neutral, however significant acid secretion occurs during the first 48 hours bringing the pH down into the more acidic range of 3.[3,20] The gastric acid secretions then stabilize for the next 10 days, after which the pH increases back to near neutral before it starts to decrease towards the normal adult pH ranges at about 3 months of age.[20] It should be noted that it is generally believed that the gastric pH levels do not fully reach adult levels until the child reaches the age of two.[4,21] The relative alkalinity of the gastric pH during this period has been speculated to be the cause of a reduced bioavailability of weak acids from enteric coated formulations.[21] Interestingly, the secretion of gastric lipase for fat absorption was also observed in the developing fetus at about 13 weeks post conception but varies during gestation in neonates, with decreasing levels observed throughout infancy.[20] These findings for the gastric pH and the secretion of a lipase will play an important role for the absorption of BCS Class II drugs dosed as immediate release formulations.

The discussion of luminal contents along the GI tract revealed that a comprehensive review or understanding of the contents as they pertain to drug release is not available. Information from digestion and absorption studies in children may provide some insight into the luminal compositions, as was highlighted by Koldovsky.[22] In addition, information on fluid and electrolyte absorption and secretion could also be used to extrapolate data on composition.[23] However, it was noted that intubations are often required to sample these *in vivo* fluids, and the risk of the procedure may be limiting. Since simulated gastric and intestinal fluids are an important factor for investigating *in vitro* formulation dissolution performance, the PBCS working group concluded that this represented a significant knowledge gap.

Changes in the regional GI physiology are also known to occur during development, which alters the epithelial cell layer's morphology, epithelial cell tight junctions, as well membrane

transporters and cellular metabolizing enzyme levels at different stages.[21,24,25] Many other resources are available that detail these changes, yet it was not clear how the developing GI epithelium acts as a barrier to absorption. We have long recognized the importance of immunoglobulin transfer from the mother to the fetus that appears to occur in the early stages of breast feeding, but very little is understood on how that would translate to the paracellular or transcellular permeation of therapeutic agents. Hence, the consensus of the PBCS working group was that there exists significant information regarding pediatric GI development in the literature, but clear links to its impact on clinical formulation performance were sparse.

Developmental changes in GI motility were also considered by the PBCS working group. While there are differences in the sucking and swallowing patterns and their coordination in the neonates to approximately 3 months of age, this was not considered to be a significant factor in drug absorption. Pharyngeal reflexes are considered important and were briefly discussed with respect to their influence on the amount of dose ingested. Taste factors were also discussed with respect to ingested dose fractions, although they were considered to fall under other working groups.

The PBCS working group primarily focused on identifying developmental changes in gastric emptying, the small and large intestinal motility, and the effects of food. From the neonatal stages to about 3–6 months of age, a majority of the gastrointestinal contents arise from either breast milk or formula. There is evidence that the gastric emptying rates appear to be slower in the preterm neonate.[26] It is also believed that the gastric emptying rates do not differ much between term infants and maturing infants in the fasted state, with the average time reported to be about one hour.[27] The effects of solid food on the migrating motor complex (MMC) involved in gastric emptying is not clear during development, although variations do exist in the fed state for adults as well.

The small intestine ranges from approximately 275 cm at birth and continues to grow and mature into adolescence, where it reaches the adult size of approximately six meters.[28] The growth rate and length of the small intestine increases most rapidly from gestation until about one year of age, after which it grows in direct proportion to the body length into adulthood. The availability of a “surplus” intestinal region required for adaptation to factors including food, environmental factors, and diseases was also determined.[28] The villus to crypt surface area does change during development, however it is unknown how this will impact drug absorption. The small intestinal motility occurs in several phases governed by the MMC in the fasted state, whereas the presence of food may have some affect on motility.[29] The length of the small intestine directly affects the small intestinal transit times, thus variability will be inherent based on the growth rate and stage of development of the child. It should be noted that average regional liquid GI transit times for a child were reported to be 1.1, 7.5, and 17–40 hrs for the stomach, small and large intestines, respectively.[30] However, these values were taken from a broad range of ages. The GI motility will also be a function of disease states, particularly in smaller children who are susceptible to GI conditions such as diarrhea.

The PBCS working group focused on the stomach and the small intestine based on their predominant roles in absorption and a general lack of understanding of colonic motility. While information is available based on the colonic development, much of the research performed on the colon is conducted under evacuated states by techniques like endoscopy.[29] It is not clear how the analysis may affect the measurements of important parameters under these abnormal physiological conditions. There was a general consensus that additional research was required to determine the physiology of the cecum and the ascending colon in

children to address the factors related to absorption from controlled formulations and their applicability to pediatric populations.

In summary, significant further research is required to better define the GI fluid pH, compositional, and volume changes during child development. There were some discussions regarding a need for further knowledge on the surface area available for drug absorption (villus region) during child development. This is important as it directly relates to intestinal permeability and absorption. Furthermore, there does appear to be a knowledge gap in our understanding of GI motility, which needs to be better evaluated and reviewed by the PBCS working group in the future. The impact of the gut microbiome on metabolism and absorption was not addressed. Additional research in these areas is encouraged, as it will directly impact age specific formulation development in a safe and efficacious manner.

ONTOGENY OF DRUG METABOLIZING ENZYMES AND TRANSPORTERS

Ontogenic changes in the expression of drug metabolizing isoforms and transporters along the gastrointestinal tract and in the liver will also impact pediatric ADME and dosage form development. For instance, a recent analysis of PK data obtained for a limited number of substrates suggested that higher, weight corrected pediatric doses (ranging from 50–100% higher) for drugs that are metabolized by CYP1A2, 2C9 and 3A4 might be required to achieve similar exposure of the active levels as those observed when the agents are administered to adults.[22] However, lower pediatric first pass hepatic metabolism was also observed in children for different substrates of these isoforms, where the role of renal clearance was also indicated to be important. Alternatively, similar weight corrected doses for adults and children may be sufficient for drugs metabolized by CYP2C19, 2D6, N-acetyltransferase 2 (NAT2), and uridine diphosphate glucuronoslytransferases (UGTs) upon similar comparisons.[22] Therefore, pediatric metabolism of different compounds may vary during development and may not be directly predicted by adult data.

The PBCS working group carefully considered the available information regarding the ontogeny of drug metabolizing enzymes and transporters during development. It became immediately clear that there was a good understanding of the developmental maturation of functional hepatic metabolism[1–3,31–39] and ontogeny of Cytochrome P450 enzymes.[40–51] Phase II enzyme ontogeny in the liver was less apparent. It was also noted that the ontogenic expression levels of the DME isoforms at the mRNA and protein levels were not established along the GI tract. Furthermore, a greater understanding of ontogenic changes in metabolism and carrier mediated transport along the GI tract is critical for evaluating absorption and intestinal first pass extraction. It was further determined that these values will be essential for building age-specific pediatric Physiology Based Pharmacokinetic (PBPK) models.

An evaluation of the literature related to ontogenic based changes in drug transporter expression and function in the developing GI tracts and liver was disappointing. It was apparent that very little is known regarding pharmaceutically relevant drug transporters. What little we do know about transporter ontogeny has been largely derived from nutrient absorption literature.[21,25,52,53] Given the relevance of transporters to absorption and disposition, it was readily apparent that this was a critical knowledge gap that required significant research.

The PBCS working group generated a list of several pertinent knowledge gaps that exist should be prioritized for future research: 1) Ontogenic changes in the expression of pharmaceutically relevant transporters along the developing GI tract, liver, and kidney need to be addressed; 2) A greater focus has to be placed on delineating the role of developmental changes in GI metabolism; 3) Incentives for descriptive research to elucidate the ontogenic expressional changes in DMEs and transporters should be considered a priority, despite the

fact that it is not the typical hypothesis-driven research normally proposed; 4) Further literature review needs to be performed to assess ontogenic changes in nuclear hormone factors that regulate DME and transporter expression in the GI tract, liver and kidney; and 5) Research on transporter mediated ontogenic Drug-Drug and Drug-Nutrient Interactions in children should be emphasized. There was also some discussion regarding the need for additional research into suitable animal models for developing investigating intestinal absorption and disposition in infants, which appears to be an area of unmet need. Finally, the requirement for tissue specimens to perform the ontogenic research on DMEs and transporters was highlighted and will be discussed below.

PEDIATRIC BIOBANKING

Towards addressing the critical knowledge gaps that exist in the ontogenic expression of DMEs and pharmaceutically-relevant transporters, high quality pediatric tissue specimens are a desperately required. Unlike adult tissue specimens, there appears to be a paucity of commercially available pediatric tissues. Furthermore, the collection and use of pediatric tissues has been hindered by the many practical and ethical considerations associated with tissue procurement from children, including a very limited population base for tissue collection. Cryopreserved tissues collected from clinical research are also often protected under extensive federal regulations required for human research, and thus sharing these tissues with other colleagues requires Institutional Review Board approval.

Currently there are new initiatives within pediatric academic settings to develop strategic and efficient BioBanks that will provide researchers with high quality tissue specimens to perform further research in this area. Table 1 provides a representative list of some pediatric BioBanks that are actively pursuing the establishment of a shared resource center (prepared by Alexander A. Vinks and J. Stephen Leeder; unpublished survey). The PBCS working group felt strongly that funding for the establishment of biorepositiories was a critical area of need. Moreover, initiatives to increase the number of healthy tissue specimens should be supported, when ethical collection is performed. There was a clear consensus that the availability of these tissues is essential, particularly for determining ontogenic expression patterns that will be required for PBPK and PopPK modeling of the absorption and systemic availability in the pediatric population. It was also concluded that these resources may help accelerate novel pediatric drug discovery and formulation design in the future.

PHYSIOLOGY- AND POPULATION-BASED PHARMACOKINETIC MODELING (PBPK AND PopPK)

Our incomplete understanding of the developmental maturation of drug disposition (PK) and drug effects (PD) poses a significant challenge to the development of age based pediatric dosing algorithms and adverse events risk assessment. Most pediatric PK data has been obtained from small parallel studies often supplemented with data derived from population-based pharmacokinetic analyses (PopPK) during the later phases of development. This data has been our primary sources for the identification of factors that would potentially explain variability in drug disposition. To fully explain underlying factors, critical missing information needs to be generated relating to the ontogeny of drug related parameters. Fundamental to this approach is the separation of information related to the ‘physiology’ (i.e. human body) from that of the ‘drug’ (e.g., physicochemical characteristics of the drug that are important for ADME) and the ‘study design’ (e.g., the physicochemical characteristics and composition of the dosage form, dosing regimen, concomitant drug(s) administration, and food effects). This quantitative ‘bottom-up’ approach includes physiologically-based *in vitro – in vivo* extrapolation (IVIVE) and has gained momentum due to our increased understanding of the contributing factors (e.g., physical chemistry,

systems physiology and pharmacogenetics) and advances in quantitative modeling using mechanistic models.[2,33,54–62]

The PBCS working group also discussed the "top-down" approach of utilizing already available pediatric clinical trial data to build PBPK and PopPK models. It was concluded that utilizing both approaches would be important to advance our research in the area. Furthermore, ten candidate compounds (Table 2) from different BCS classifications were selected based on the availability of pediatric clinical data, the differences in absorption and disposition, the potential for metabolic and transporter effects, and the ability to develop model databases that can combine both the bottom-up and top-down characteristics required for validating a model. It was agreed that we would continue to perform comprehensive data searches to further identify compounds for enhancing the predictive power of the models.

PEDIATRIC BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS has been a valuable tool for granting biowaivers for both innovator and generic pharmaceuticals for waiving in vivo human clinical testing and for making rational drug and formulation selections based on the BCS Class.[10–13] The PBCS working group was established with the primary goal to identify critical information that was required in order to establish the age specific classification systems for children. In our evaluation we revealed that some supportive literature required to assess age specific, pediatric intestinal absorption did exist. However, we also came to the realization that there were numerous knowledge gaps that needed to be filled. It was readily apparent that the BCS needs to be updated for pediatric use. We present some of the additional issues that will need to be addressed in order to develop and refine the PBCS.

Information on well-known excipients is available (for example, monographs and the FDA's inactive ingredients guide US FDA CEDs Inactive Ingredients [IIG]) to select appropriate excipients from adult formulations. For new excipients, a battery of FDA-approved tests is needed. However, there are challenges in selecting pediatric excipients (for example, there is no pediatric IIG). A pediatric IIG needs to be developed to help with age-specific formulation studies. Choice of excipients and their related toxicity needs to be justified for inclusion. Novel approaches exist to mask the taste with an ability to find the exact amount of excipient needed in a real-time fashion. This should prevent the overuse of excipients. Once the taste is masked completely, other organoleptics may be added judiciously. For neonates and very young children, it is always a good idea to use the least amount and number of excipients.[72]

One of the challenges to compounding drugs is the composition of extemporaneous compounding vehicles. Pharmacy practice guidelines list excipients that should not be used in liquid formations, yet some compounding vehicles contain banned excipients (for example, propylparaben). In addition, because many drugs are bitter, taste masking is needed to improve palatability and acceptability. Strategies to taste mask liquid dose forms include (1) complexation, sweeteners, and flavors for solutions/syrups and (2) salt forms, coatings, sweeteners, flavors, and viscosity builders for suspensions. Assessing the critical quality attributes of the extemporaneously compounded products will be required to ensure reproducible performance in the different age based populations.[7] Tests to measure performance will also need to be developed in a straightforward manner with consideration towards the potential global clinical utility of the compounded formulations.

Is There a Need for a Pediatric BCS?

In a new era of molecular ADME, the BCS focuses on "A" (absorption), whereas the BDDCS focuses on "DME" (distribution, metabolism, and excretion). Both the BCS and the

BDDCS are needed for pediatric formulations, with an emphasis on bioavailability (BA) and bioequivalence (BE). The basis of the BCS is drug permeability and solubility and drug product dissolution. In the BCS, the approach for determining solubility is a drug's minimum solubility in water over the range pH 1 to pH 7.5 at the highest dose and 250 milliliters (ml) of water. If a drug's highest dose strength dissolves in 250 ml (8 oz) of water, then it meets the FDA definition for a high solubility drug. In standard adult BE studies, drug products are administered in 250 ml of room-temperature water in a fasting state. A pediatric BE standard has not been established, however, and a recommendation in this area is needed. There also needs to be a more predictive *in vivo* dissolution test. Such a dissolution test would make the development of pediatric dosage forms much simpler.

Another issue regarding drug BA in pediatrics is whether the BA is similar to that in adults. The BA should be optimized in developing new pediatric drug products. BE involves two products with the same drug for which the PK parameters are similar between the formulations. With this in mind, a reference dosage form could be established for pediatric product testing in order to ensure quality and performance at least in vitro. This would allow one to assess substitutable pediatric products. Clearly there needs to be a validated *in vivo* dissolution method developed that will that demonstrate that the fraction dose available of absorption is the same from each product in the same time dependant manner. A suitable animal model surrogate may be useful in this case. The BCS focuses on the fraction absorbed. Systemic availability, which includes first–pass metabolism and fraction absorbed, is the upper limit to systemic exposure.

The role of dissolution testing is as a quality control assessment, that is, the detection of product changes. There needs to be an *in vitro* test for *in vivo* product performance to be used in formulation development and BE testing, especially for the pediatric populations. A new drug dissolution paradigm is needed where (1) similar plasma levels equate to similar PD, (2) similar *in vivo* dissolution equates to similar plasma levels, and (3) similar *in vitro* dissolution equates to similar *in vivo* dissolution. The best *in vitro* dissolution test (for example, *in vitro–in vivo* correlation) needs to be determined. Both permeability and solubility need to be part of any new paradigm.

The PBCS working group concluded that there are differences between the utility of currently administered pediatric products from the development of new products. For current products where there exists a therapeutic interchangeability, the BCS and BE can be used in many instances. For new products, it should be reiterated that the BDDCS and the BCS should be used where the BCS focuses on "A" (absorption), whereas the BDDCS focuses on "DME" (distribution, metabolism, and excretion). The BDDCS divides compounds into four classes based on their permeability and solubility.[17–19,73] The BDDCS classification system is useful in predicting effects of efflux and uptake transporters on oral absorption as well as on post-absorption systemic levels following oral and intravenous dosing.

Both the BCS and the BDDCS are needed for pediatric formulations, with an emphasis on bioavailability (BA) and bioequivalence (BE). Plasma levels of drug and metabolite(s) depend on dose rate. *In vivo* dissolution, or whether it can be reflected in correlative *in vitro* dissolution methods, is the critical factor. If there is the same dissolution rate, there will be the same absorption rate and metabolism rate in a given age group. If a drug product's *in vivo* dissolution is the same, the same plasma levels will result (that is, the same fraction absorbed, the same metabolism). It is acknowledged, that this will be age and classification specific for each compound.

Issues Raised by the PBCS Working Group

To summarize, there are differences between current products and new products. For current products and therapeutic interchangeability, the BCS and BE can be used. For new products, the BDDCS and the BCS can be used. Plasma levels of drug and metabolite(s) depend on dose rate. *In vivo* dissolution, or whether it can be reflected in *in vitro* dissolution, is the critical factor. If there is the same dissolution rate, there will be the same absorption rate and metabolism rate. If a drug product's *in vivo* dissolution is the same, the same plasma levels will result (that is, the same fraction absorbed, the same metabolism).

Dr. Gordon Amidon tentatively proposed the following BCS classification:

- Class 1: (pediatric, volume = 25 ml): rapid dissolution (t_{50}= 15 min.) for immediate release
- Class 2: (Subclasses a,b,c for acids bases and neutral): Dissoution criteria are critically needed
- BCS Class 3: very rapid dissolution.
- BCS Class 4: Same as BCS Class 2.

He also proposed that a BE/BA dissolution scheme based on the BCS class, and drug solubility at pH 6.8, drug product dissolution at pH 6.8, and drug permeability. Preferred dissolution procedures can be proposed for each BCS class. He concluded that, for both BA and BE, a better *in vivo* dissolution methodology is urgently needed.

The following issues and topics regarding the biopharmaceutical issues presentations were discussed:

- The challenges for BE, BA, and *in vivo* dissolution studies in adults
- The need for studies to develop better predictive capabilities for new chemical entities
- The use of BA for new chemical entities
- The use of BE for currently marketed products
- Differences in BE/BA issues between adults and pediatrics
- The lack of knowledge of pediatric GI tract physiology and gastroenterology
- Patient-to-patient variability in pediatric populations
- Patient characteristics, disease state, and pharmacogenomics.

Several of these issues were discussed in more detail in the preceding sections. However, it is important to highlight that the interplay of these factors will affect drug- and age-specific performance in pediatric patients. Finally, the PBCS working group agreed to establish a list of 50 most utilized pediatric drugs for which there are indications or labeling, classify those drugs, and evaluate the classifications based on available pediatric PK literature.

Action Plan

The top 50 pediatric drugs will be classified for absorption, intestinal lumen brush border metabolism, metabolizing enzymes that affect intestinal first pass metabolism, and hepatic first-pass metabolizing enzymes that limit systemic availability. Most of this information may not be readily available, but efforts will be made to search all available literature through collaboration with the National Library of Medicine staff. A subgroup was also

established to review the current gaps in knowledge in ADME that affect pediatric drug bioavailability, which was highlighted in preceding sections.

The next step will be to identify for each drug what is known from adults. The focus will be on factors that may be limiting the fraction absorbed and systemic availability. The PBCS selected ten compounds (Table 2) based on factors including their BCS classification, disposition and the availability of pediatric trial data for modeling. Simulation studies will be conducted for the ten selected compounds using both the bottom up and top-down approaches as mentioned above. It is anticipated that the metabolism information sources will be from both *in vitro* and *in vivo* studies. Pediatric information of interest includes GI volume, GI motility, age specific variations, established hepatic metabolism, and DME and transporter ontogeny, if possible. Formulation variability may also be introduced in specific cases to determine if excipients alter BA. For example, whether taste masking alters the BA of BCS Class 1 and Class 3 drugs. Taste masking information on BCS Class 3 drugs may be more important.

CONCLUSIONS

The PBCS working group evaluated the available pediatric literature and identified critical knowledge gaps that may potentially hinder the development of age specific classification systems for children. It was determined that additional research was required to fully address the gaps in our understanding of GI fluid composition, GI motility, and the pH ranges encountered along the GI tract during development. It was not clear if this information exists in literature, although these parameters will need to be defined in order to advance the PBCS based on understanding *in vivo* stability and dissolution. Moreover, the absorptive surface area along the GI tract also needs to be defined.

With respect to metabolism and drug transport, it was determined that the ontogeny of GI drug metabolizing enzyme and transporter isoforms is largely unknown. This represents a critical gap in our understanding and may necessitate focused descriptive research to enhance intestinal absorption prediction. Liver DME ontogeny has been inferred from clinical studies and is fairly well understood, although the ontogenic expression of several DME isoforms needs to be addressed. There is evidence that some of the CYP ontogeny has already been established. Hepatic drug transporter ontogeny was largely unidentified and also remains a critical area of need.

The requirement to establish ontogeny of DME and transporter ontogeny in these tissues will largely be unmet without the availability of biobanked healthy tissues. This is also a major area of need despite current efforts by researchers to catalog and share their available tissues in existing biorepositories (Table 1). This issue cannot be understated, since many of the current repositories contain specimens collected from diseased organs. These tissues are important for understanding PD, but would be questionable for use in normal physiological assessment of ontogeny. Furthermore, the ontogenic expression and functional of DMEs and transporters will be critical for the design of PBPK and PopPK modeling programs that are significantly relied upon in current pediatric clinical testing. The value of PK modeling will also be realized in both the bottom-up and top-down approaches for predicting the PK of new chemical entities across pediatric populations. Ten widely used pediatric compounds were recommended for initiating the development of pediatric PK modeling (Table 2).

It was also decided that in order to establish a rigorous pediatric biopharmaceutics classification system the adult BCS will have to be modified. The primary suggestion was to integrate the BCS for absorption with the current BDDCS to identify age dependent differences in disposition, particularly ontogenic intestinal metabolism and transporter

effects. Novel formulation and physicochemical approaches can also be used to yield products with reduced doses for pediatric populations, which is an important challenge for global communities. An action plan was developed to begin classifying the top 50 pediatric drugs with available clinical data. It was concluded that by using a collaborative multidisciplinary approach, specific drug formulations can be developed for all ages within the pediatric population.

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Table 1

Available resources and BioBanks providing access pediatric tissues.

1	NICHD Brain and Tissue Bank for Developmental Disorders at the University of Maryland, Department of Pediatrics at Baltimore.
	• The NICHD Brain and Tissue Bank (BTB) for Developmental Disorders are contracted to the Eunice Kennedy Shriver National Institute of Child Health and Human Development. In 1991, NICHD funded a Brain and Tissue Bank for Developmental Disorders at the University of Maryland, School of Medicine, Baltimore, MD. in 1992. The BTB repository site and has a contract to solely operate the facility for the NICHD until 2014.
	• The mission of the NICHD BTB is to advance the research of developmental disorders. The objective of this human tissue repository is to systematically collect, store, and distribute brain and other tissues for research dedicated to the improved understanding, care and treatment of individuals with developmental disorders.
2	National Cancer Institute.
	• The Cooperative Human Tissue Network (CHTN), Pediatric Division is a group of six member institutions, supported by NCI, that collect and distribute tissue to researchers across the United States and Canada. Since its establishment in 1987 the CHTN has provided more than 500,000 high quality specimens from a wide variety of organ sites to over a thousand investigators.
3	Children’s Oncology Group (COG).
	• The COG Biopathology Center (BPC) at The Research Institute of Nationwide Children’s Hospital maintains the largest pediatric specimen bank in the nation. The BPC houses the COG Solid Tumor Tissue Bank, Pathology Center and the Acute Lymphoblastic Leukemia and the Neuroblastoma Reference Laboratories.
4	Other repositories at individual sites:
	• Children’s Mercy Hospitals & Clinics
	• Cincinnati Children’s Hospital Medical Center
	• Children’s Hospital of Wisconsin
	• Biorepository at Emory + Children’s.
	• CHOP Cancer program.
	• Duke. Pediatric Brain Tumor Foundation Institute at Duke

Table 2

Selected compounds for bottom-up and top-down PBPK and PopPK model building.

Compound	Solubility (mg/mL in water)	Permeability (10^{-4} cm/s)	Transporters	Drug Metabolizing Enzymes[63]	Measured Log $P_{O/W}$	Dose Number	Adult BCS	BDDCS[18]
Acetaminophen	23.7		MRP1/5, BCRP?/Pgp	SULT and UGT isoforms; CYP1A2/2E1 and CYP3A4[64]	0.2	0.2	3,4[64]	1
Amoxicillin	3.5	0.3[67]	PepT2?; OAT isoforms; Pgp combination therapies?[68]	Not apparent in humans.	0.87	1	1,4[65,66]	3
Azithromycin	39		Pgp?	Not apparent in humans.	4.02	0,06	4	3
Carbamazepine	0.256	4.3 ± 2.7[67]	MRP2, Pgp? Induces MRP and Pgp	3A4/5/7 Induces CYP1A2[69], CYP2C19, 3A4/5/7?	2.45	4.7	2, 2(WHO)	2
Cefdinir			?				4, 4[65,66]	4
Methylphenidate					1.80		2, 2[65,66]	1
Midazolam	10.3		Inhibits and induces Pgp	CYP 3A4/5/7	3.27		1	1
Omeprazole			Pgp Inhibits Pgp, BCRP	CYP 2C19, CYP3A4 (possible small contributions from CYP2C9, CYP2A6, CYP2D6)[70]	2.23		2	1
Phenobarbital	1		Induces Pgp	Induces CYP2B6, CYP 3A4/5/7	1.47	0.2	1, 4(WHO)	1
Valgancyclovir	70		PepT1	BPHL[71]	−2.05	0.03	3	1

(WHO)-from World Health Organization