Best Pharmaceuticals for Children Act
Pediatric Formulations Initiative Workshop
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Bolger Center
Potomac, MD

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Meeting Objectives

The purpose of the meeting was to review the range of issues and challenges in creating pediatric formulations as well as discuss the current gaps in knowledge and technological advances. The specific objectives were to summarize current knowledge, harmonize and develop new approaches to address identified challenges, and identify cutting-edge formulations in adults that have applicability in pediatrics. The meeting participants reviewed the work of the individual Pediatric Formulations Initiative (PFI) working groups, added any new issues, prioritized issues, and discussed ways to stimulate further research in the field.

Day 1

Workshop Introduction

Anne Zajicek, M.D., Pharm D., Chief, OPPB, CRMC, NICHD, NIH

The purposes of good pediatric formulations are accurate dosing, adherence to the prescribed therapeutic regimens that are palatable and easily administered, improved safety of patient and caregiver, and improved therapeutic outcome.

Dr. Zajicek explained that the first BPCA legislation was enacted in 2002 and the second in 2007. The BPCA of 2002 mandated that the NIH (1) create a master list of all off-patent drugs that lack adequate pediatric labeling and (2) develop, prioritize, and publish an annual list of drugs in need of reformulation. The BPCA of 2007 mandated that the NIH (1) develop, prioritize, and publish an annual list of therapeutic areas and (2) prioritize therapeutic gaps, potential health benefits of research, and adequacy of necessary infrastructure.

Although there are established industry processes for developing adult drug formulations, there are no such processes for developing pediatric drug formulations. To address this issue, the NIH implemented three initiatives: the Pediatric Trials Network (PTN), the Formulations Platform 2010–2012, and the PFI. In 2010, the OPPB awarded a contract to Duke University to develop the infrastructure for the PTN. The core tasks of the contract are

- PTN management
- Clinical trials performance

- Formulations development for clinical trials
- Clinical pharmacology study design and analysis
- Device development and validation.

An interagency agreement between the NIH and the U.S. Food and Drug Administration (FDA) established the Formulations Platform Initiative 2010–2012 to (1) provide an open source, publicly available oral pediatric formulations platform and (2) designate specific formulations technologies, given the molecular and chemical properties of the drug and the specific desired properties of the dosage form.

In the 2011 PFI Workshop, four working groups were asked to prioritize short-, mid-, and long-term goals in the following areas:
- Biopharmaceutics
- Taste and flavor
- Biopharmaceutics Classification System (BCS)
- New technology and drug delivery systems.

Workshop Overview

George Giacoia, M.D., Program Scientist, OPPB, CRMC, NICHD, NIH

The PFI was formed by the OPPB in 2005 to address the lack of appropriate formulations as mandated by the BPCA of 2002 and 2007. The purpose of the PFI is to identify and address the scientific, regulatory, and economic barriers that prevent the development of pediatric formulations and review current gaps in knowledge. The PFI does this by facilitating interactive discussions, data sharing, and feedback between industry, academia, regulatory agencies, and funding agencies.

The overall goal of the PFI is to develop a blueprint to address issues related to pediatric formulations needs including gaps in knowledge, solutions to identified problems, and types of research innovations needed. The blueprint will serve as a guide for future interactions (both national and international), development of research initiatives and programs, and identification of funding needs and sources. Specific objectives to achieve the overall goal will be determined by technical focus groups that will analyze the issues, determine priorities, and develop a set of individual recommendations and action items.

The 2011 PFI working groups are as follows:
- **Biopharmaceutics Working Group.** This working group reviews new approaches to pediatric formulations development by transforming an empirical process to a scientific-based platform, identifies taste masking technologies appropriate for children, and evaluates new concepts in pediatric formulations design.
- **BCS Task Specific Group.** This working group focuses on the development of a framework to close the knowledge gap on the effects of developmental changes on drug disposition for selected Biopharmaceutical Drug Disposition Classification System (BDDCS)/BCS Class 1–4 drugs in pediatrics. A major goal of the working group is to validate the use of the BCS and the BDDCS in children.

- **New Technology and Drug Delivery Systems Working Group.** This working group stimulates the development or application in pediatrics of new methods of drug delivery, the adaptation to pediatrics of new technologies (for example, nanotechnology), and the development of pediatric-specific devices.
- **Economics Working Group.** This working group identifies economic barriers, reviews reasons for failure of pharmaceutical companies dedicated to reformulation of off-patent drugs, and identifies possible economic incentives. In addition, the working group explores possible funding mechanisms and the development of academic and industry partnerships to create cost-effective and appropriately formulated products for orphan and off-patent drugs and ensure their distribution and availability.
- **Taste and Flavor Testing Working Group.** This working group summarizes current knowledge of drug palatability and promotes the development and/or harmonization of age-appropriate standardized psychophysical methods for testing drug formulations in children and adult panels, proposes the development of *in vitro* and animal models to predict the degree of bitterness likely to be sensed by children, and recommends research aimed at increasing understanding of the intracellular mechanisms of bitter taste signaling.

Each working group will (1) develop an issues analysis framework to capture known information and identify gaps; (2) determine and prioritize the key issues and translate these into short-, mid-, and long-term goals; and (3) develop action plans and deliverables to implement the goals.

According to its prioritization guidelines, the PFI will
- Maximize interdisciplinary collaborations and interactions
- Balance priorities for basic and applied research
- Consider NIH, FDA, other agencies', and foundations' funding initiatives
- Harmonize with the activities of other organizations (for example, the World Health Organization [WHO], the European [EU] PFI, and EU research initiatives)
- Tackle "low hanging fruit" opportunities first.

Possible PFI outcomes include:
- Publication of proceedings from the output of each working group
- Publication of review articles, white papers (on the state of the art), and approaches to study designs
- Development of a prioritized strategic approach to address uncovered gaps in knowledge (link with the NIH, industry, other federal agencies, foundations, and sponsorships)
- Development of a blueprint to address long-standing issues in collaboration with industry
- Development of mechanisms to foster research involving academia and industry
- Development of collaborations with groups and organizations committed to improving the availability of pediatric formulations and fomenting scientific advances in formulation research and adherence to pediatric formulations (for example, the WHO, the EU PFI, the Clinton Foundation, the Gates Foundation, and the Lucile Packard Foundation).

Biopharmaceutical Issues: Global and Scientific Platforms

Global Platform Technology for Flexible Dosing and Solid Dosage Forms

Peter York, Ph.D., Professor of Physical Pharmaceutics, School of Pharmacy, University of Bradford, United Kingdom

Drug delivery is the method or process of administering a pharmaceutical compound to achieve therapeutic benefit. The method must deliver the right amount at the right time to the right tissue. Pediatric medicines are not solely focused on chemistry and biology. There are issues of compliance, safety of patients, needs and capabilities of medical staff and care, and implications for the development of suitable medicines for children. The dosage forms that are likely to prove most suitable are flexible solid dosage forms. For oral medicines requiring precise dosage measurement, the most suitable dosage form should be based on use of a solid platform technology (for example, a multi-particulate solid) with tailored dosage strengths and a range of dosage forms.

Addressing short-term needs requires the innovative application of existing technology rather than the introduction of innovative technology. Multi-particulate systems (that is, base solid form) can provide a flexible platform for dosage form design across pediatric age groups. One approach to developing a solid drug product involves the following steps:

- Select pediatric-appropriate excipients to enable preparation of base solid
- Form a base solid unit
- Define the drug-excipient ratio
- Convert base solid units into final dosage form
- Add excipients to prepare final (alternative) oral dosage form
- Package and label to address the end-user's needs.

A widely used, well-understood technology can be used; an innovative technology is not required. Using a current technology allows uniformity and flexibility in dosage, as well as alternatives to the final solid forms. Such an approach can address short-term needs and can be applied to both on- and off-patent active pharmaceutical ingredients (APIs). The approach also allows incorporation of new knowledge (for example, absorption, distribution, metabolism, and excretion [ADME]; pharmacokinetics [PK]; and pharmacodynamics [PD]) into the design of base forms as it becomes available.

Multi-particulate base forms can be used to treat global pediatric diseases such as malaria. The single-component development process can be adapted to a two-component granule dosage form of artesunate and amodiaquine. Different granule blend ratios of these two drugs can provide the flexible dosage required for all groups of pediatric populations to address end-user requirements. Flexible dosage form systems can be used to develop alternative dose levels and drug ratios.

Flexible, simple dosage forms based on multi-particulates (for example, granules and pellets) can be developed. Well-understood technologies can be used in innovative ways. Basic form or secondary processing into a range of solid dosage forms provides flexibility for dose. Taste masking can be incorporated, and local variations are possible. Age-related solid oral pediatric

medicines for major diseases can have a global impact. Multi-particulate systems can be applied to fixed-dose as well as variable ratio drug combinations. Robust architecture enables improvements informed from new knowledge. Future scenarios include molecular biology for taste masking; the use of polymeric systems for sustained, delayed, and gastro-retentive release; dividable strips; and a wider range of excipients in neonates and infants to deal with challenging molecules.

Scientific Approach for the Development of Pediatric Formulations

Mansoor Khan, Ph.D., Director, Division of Product Quality Research, Center for Drug Evaluation and Research (CDER), FDA

In the preformulation phase, many studies of physical and chemical properties must be conducted for all adult formulations. Similar studies must also be conducted for pediatric formulations. Although the results of the adult studies can often be applied to pediatric formulations, preformulation studies are needed when developing new pediatric drug products. The drug industry has well-established processes for drug development that include (1) drug discovery and preclinical research (before investigational new drug application), phase I–III clinical trials (before new drug application [NDA]), NDA review, and FDA filing and approval. The challenges for developing pediatric liquid dosage forms (for example, solutions) include solubility, stability, taste masking, and appropriate selection of excipients and packaging materials. Typical ingredients may include solubilizers, stabilizers, viscosity builders, sweeteners, colorants, flavors, or complexing agents. Selection of ingredients can be critical depending on BCS classification.

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. In conjunction with dissolution of the drug product, 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. BCS Class 1 drugs have high solubility and high permeability. BCS Class 2 drugs have low solubility and high permeability. BCS Class 3 drugs have high solubility and low permeability. BCS Class 4 drugs have low solubility and low permeability. The selection of excipient depends on the BCS classification of the drug. Drug development strategies can be determined by BCS classification and excipient effects. For poorly soluble compounds, solubilization methods include salt formation, complexation, surfactants, cosolvents, nanosizing or micronizing, and amorphous or high-energy compounds. Information on well-known excipients is available (for example, monographs and the FDA's inactive ingredients guide [IIG]) to select appropriate excipients. For new excipients, a battery of FDA-approved tests is needed. There are challenges in selecting pediatric excipients (for example, there is no pediatric IIG).

One of the challenges to compounding drugs is the composition of compounding vehicles. Pharmacy practice guidelines list excipients that should not be used in liquid formations, yet some compounding vehicles contain banned excipients (for example, propylbaraben). 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.

Using a collaborative multidisciplinary approach, products can be developed for all ages within the pediatric population. Choice of excipients and their related toxicity needs to be justified for inclusion. The BCS needs to be updated for pediatric use. A pediatric IIG needs to be developed to help with pediatric formulation studies. 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 go with the least amount and number of excipients. Novel approaches can also yield products with reduced doses on a molecular basis.

Is There a Need for a Pediatric BCS?

Gordon L. Amidon, Ph.D., Charles R. Walgreen, Jr., Professor of Pharmacy, Professor of Pharmaceutical Sciences, College of Pharmacy, University of Michigan

In a new era of 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 permeability and absorption. Drug product solubility and permeability are the limiting factors for absorption. 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. If a drug's highest dose strength dissolves in 250 milliliters (ml) 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. There needs to be a more predictive *in vivo* dissolution test. Such a dissolution test would make the development of pediatric dosage forms simpler.

One 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 is the same for the two drug products. However, a reference dosage form needs to be established for pediatric products. To have substitutable pediatric products, there needs to be an *in vivo* dissolution to ensure that the fraction absorbed is the same. The BCS focuses on the fraction absorbed, which includes first pass metabolism and systemic availability. Absorption is the upper limit to systemic availability. The current BE paradigm is (1) similar plasma levels equate to similar PD, (2) similar *in vivo* dissolution equates to similar plasma levels, and (3) *in vitro* dissolution equates to *in vivo* dissolution.

The role of dissolution testing is quality control, 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 studies. 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.

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. Amidon proposed the following BCS/BDDCS classification

- Class 1 (pediatric, volume = 25 ml): rapid dissolution for immediate release and modified release
- Class 2a: limited first-pass metabolism
- Class 2b: unknown
  Class 2c: *in vivo* gastrointestinal (GI) tract processes (bile salts/transit)
- BCS Class 3: very rapid dissolution.

Dr. Amidon also proposed a BE/BA dissolution schema based on the BCS class, drug solubility at pH 1.2, drug solubility at pH 6.8, and drug permeability. Preferred dissolution procedures were listed for each BCS class. He concluded that, for both BA and BE, better *in vivo* dissolution prediction is needed.

Question and Answer/Discussion Session

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.

New Technology and Drug Delivery Systems

Dendrimer-Based Targeted Nanotherapeutics: Applications in Pediatric and Neonatal Neurodegenerative Diseases

Rangaramanujam M. Kannan, Ph.D., Professor of Ophthalmology, Center for Nanomedicine/Wilmer Eye Institute, Johns Hopkins University School of Medicine

Dendrimers are tree-like, multifunctional, single-molecule, nanostructured polymers (~ 5–10 nanometers). They have both molecular and nanostructural features. They are biocompatible, noncytotoxic, and cleared intact from circulation. The specific dendrimers of interest are hydroxy-terminated generation-4 poly(amido amine) (PAMAM) "neutral" dendrimers, with beta-alanine repeat units (peptide-like). The amide-amine-hydroxy structure is desirable for intracellular pharmaceutics. There are a variety of functional units on the molecule surface to which drugs, targeting ligands, and imaging agents can be attached at the same time. The specific structure of the dendrimers may be related to their effects, but it is not clearly understood why dendrimers exert their effects. Double-check the strategy of studies is to use the unique interaction between PAMAM dendrimers (no ligands) and disease pathology such as neuroinflammation. The targeted cells are activated microglia and astrocytes, which are implicated in periventricular leukomalacia and cerebral palsy (CP).

In a rabbit model of CP, intrauterine injection of bacterial endotoxin lipopolysaccharide resulted in a neurobehavioral phenotype of CP. Endotoxins resulted in neuroinflammation and neuronal impairment in dendritic branching, organization, and decreased spines. The intrauterine administration of endotoxins leading to motor deficits in the rabbit model has shown a link between prenatal infection and CP. Several studies showed that intravenously injected dendrimers preferentially localize to activated microglia and astrocytes in the rabbit CP model. With subarachnoid injection, dendrimers also localize to activated microglial cells in rabbit brains with neuroinflammation, far removed from the site of injection. The dendrimers are short-circulating, hydrophilic, and about 15,000 daltons. For typical blood-brain barrier (BBB) transport, there needs to be a long circulation time, lipophilicity, and small molecular size. Although it is not known exactly how the dendrimers cross the BBB, animal models of CP show an impaired BBB.

A study was conducted to determine whether dendrimers can be used to deliver therapeutics in a targeted manner. The study drug was N-acetyl cysteine (NAC), which is a widely used drug with extensive clinical safety data in pregnant women and preterm infants. NAC has antioxidant and anti-inflammatory properties and replenishes glutathione. The study hypothesis was as follows: If postnatal dendrimer-NAC therapy leads to motor function improvements, the same treatment may prevent CP, when administered to the fetus combined with early diagnosis. The results showed that intrauterine administration of dendrimer-NAC drastically improved neurobehavioral impairments from postnatal day 1 to day 5 in the rabbit model, suggesting phenotype reversal. Dendrimer-NAC reduced inflammation at the cytokine and protein levels and oxidative stress by targeting proinflammatory microglia. Dendrimer-NAC improved myelination organization, neuronal branching, and neuronal injury.

The results suggest that there may be an important therapeutic window of opportunity right after birth for treating CP, which is currently being missed. Single intravenous administration of dendrimer-NAC postnatally may be able to provide sustained attenuation of motor deficits. Intrinsic targeting (no ligands) results in the delivery vehicle performing better in this central nervous system application than in tumor xenografts with ligands. Targeted therapy can prevent or arrest fetal neuroinflammation. Dendrimer-based nanotherapeutics provides a platform for delivering drugs in a targeted, sustained manner for brain injury.

In conclusion, dendrimers have unique *in vivo* properties (targeting neuroinflammation). The hydroxyl-terminated dendrimers were noncytotoxic in newborns and pregnant mothers (rabbits) even at 550 mg/kg. Taking advantage of the structural and functional aspects of dendrimers can lead to improved targeted therapeutic outcomes in CP.

Remotely Triggerable Drug Delivery Systems

Daniel Kohane, M.D., Ph.D., Associate Professor of Anesthesiology, Department of Anesthesiology, Children's Hospital Boston

On example of a conventional drug delivery system is a drug-eluting contact lens, which allows prolonged drug release. This system has relatively zero order of kinetics. Drug release can only be modulated by taking out the contact lens. A second example is multi-lamellar liposomes that are filled with saxitoxins (STX), which are potent neurotoxins but also a very potent local anesthetic. Injection of STX-dexamethasone liposomes in the sciatic nerve in rats can block nerves for up to a week. However, once the liposomes are injected, their effect cannot be modulated.

With local (passive) triggering, the body or local phenomenon (for example, pH or enzyme concentration) determines when the drug is released—not the patient, physician, or algorithm (closed-loop).

Remote (active) triggering allows precise control of timing, duration, dosage, and location of drug release by the patient, doctor, or algorithm (closed loop). A key concept is on-demand drug delivery. This approach is convenient and improves efficacy and therapeutic index. Remote triggering can be applied to treatment of pain (local and systemic anesthesia), diabetes, endocrine conditions, cancer, and "chrono-administration." Triggerable drug release devices can be on a macroscale but are usually on a nanoscale. The devices can be intended for local or systemic use, depending on the design. If they are nanoscale, they can take advantage of the fact that some conditions such as tumors or damaged tissues have enhanced uptake of nanoparticulate structures. The disadvantage of nanoscale delivery is that the drug tends to leave the site if injected locally and tends to end up in the reticuloendothelial system. Another disadvantage of nanoscale devices is that they may only be able to deliver one dose. However, they are usually injectable. Locally delivered devices (depot) can be any scale, but tend to be larger. Drug can be intended for local or systemic use and tends to stay where placed. Advantages are large amounts of drug can be put into the device and multiple doses can be delivered. However, the effects can be disastrous if the devices break. They may require reimplantation. Other considerations for locally delivered devices are power sources, biodegradation, biocompatibility, fouling, and

infectious risks. Remote triggers include electricity (microchips), light (ultraviolet, near infrared, visible), magnetism (static or oscillating), and ultrasound.

Leveraging Nanotechnology for Patient-Tailored Treatment of Serious Pediatric Illnesses

Fatih Uckun, M.D., Ph.D., Professor Research Pediatrics, Children's Hospital Los Angeles

Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer. With the progressive intensification of therapy, more than 80 percent of children with ALL achieve long-term survival. To achieve this level of cure, children are exposed to very intensive therapies that have serious short- and long-term toxicities. Relapses occur across all risk groups, and only 30 percent of children who relapse survive. Nearly 30 percent of children with ALL with "high-risk" features have failed to respond to therapeutic intensification and require new therapeutic approaches for cure. The challenge for treating these children is to uncover the underlying genetic abnormalities in this resistant form of disease and identify new targets for therapy.

Spleen tyrosine kinase (SYK) is a molecular target for therapy of many serious illnesses. Current SYK research focuses on assessing and developing inhibitors of this enzyme to treat a variety of diseases, including leukemia, B-lymphoma, carcinoma, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis. Although the therapeutic target (SYK) is the same, its function is relevant to many different tissues. SYK's expression and contribution to drug resistance makes it an interactive target in cancer populations. SYK has more than one function. Because SYK regulates anti-apoptotic signal transduction pathways, its inhibition would have consequences that might be of therapeutic benefit for a number of diseases. Studies have shown that SYK induction is associated with a signature transcriptome. SYK induction triggers expression of anti-apoptotic genes. Because SYK serves as a master regulator of radiochemotherapy resistance in B-lineage lymphoid malignancies, inhibition of this enzyme would prevent apoptosis.

A number of characteristics make C-61 a candidate for a novel SYK P-site inhibitor. C-61 inhibits recombinant SYK in cell-free kinase assays, inhibits SYK in B-precursor leukemia cells, and induces apoptosis in chemotherapy-resistant B-precursor leukemia cells. In addition, C-61 has shown greater anti-leukemic potency against primary ALL cells compared with other anti-leukemic drugs. Current research is focusing on (1) development of C-61 nanoparticle constructs against B-lineage leukemias and lymphomas and (2) preclinical proof-of-concept studies. These studies include efficacy studies in NOD/SCID xenograft models of leukemia, toxicity studies in mice and rats, and PK/PD studies in cells and animals.

Question and Answer/Discussion Session

The following issues and topics were discussed:

- The need for proactive approaches for pediatric drug development and disease treatment
- The need to identify barriers to implementing nanotherapeutics to the next stage
- Holistic approaches, which include profit as a motive, for conducting large scale trials
- The increasing complexity, challenges, time, effort, and costs to develop new technologies

- The application of nanotechnologies for broadly available (that is, whole body) drugs
- Patent-protected drugs as a barrier to industry partnerships.

Delivery of Inhaled Drugs for Children: Present and Future

James Fink, Ph.D., R.R.T., F.A.A.R.C., F.C.C.P., Adjunct Professor, Division of Respiratory Therapy, School of Health Professions, Georgia State University

Optimizing aerosol therapy in pediatrics and neonates depends on seven steps:
- Evaluating the patient
- Selecting the right aerosol generator
- Selecting the right interface
- Knowing what to do with crying/distressed children
- Using the right technique
- Educating the clinician, patient, and parents
- Assuring patient compliance.

Factors such as airway size, respiratory rate, flow, breathing patterns, and lung volumes create substantial challenges for effective aerosol delivery at each stage of development. Aerosol device selection is critical for therapeutic effectiveness and adherence. Poor choices may simply not provide benefit or not be used. Aerosol device options for infants and small children are limited to nebulizers with mask, nebulizers with low flow nasal prongs, and pressurized metered-dose inhalers with a valved holding chamber and mask. Passive dry powder inhalers are not acceptable. Device selection depends on the age and size of patients and their ability to cooperate and tolerate therapy. Determining aerosol dose for infants is important. However, attempts to adjust the dose simply by body weight do not stand up to scrutiny. Infant and pediatric doses also differ from adults. Dose adjustments are largely based on opinion versus evidence. Masks are often the devices that bridge aerosol devices designed for adults to infants. Although children younger than 3 years may not reliably use a mouthpiece, masks have been the primary alternative for infants and small children. Studies suggest that clinical efficacy is similar for aerosol delivery with both facemask and mouthpiece.

Good aerosol therapy to infants and small children can be improved. Areas include new devices that work across pediatric patient age and size, effective interfaces designed for use with each age and size, improved uniformity and standards for *in vitro* testing, and rational guidelines for demonstrating efficacy and safety in the smallest of patients. Proper device selection, a good interface between aerosol generator and patients, and a relaxed, quietly breathing patient can greatly improve not only the effectiveness of therapy but the willingness of infant, child, and parent to continue therapy.

Pediatric Adherence: Research Update

Dennis Drotar, Ph.D., Professor, Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center

Large numbers of children and adolescents have chronic physical conditions (20–25 percent) or behavioral problems (17–22 percent) that require treatments that need to occur over a long period

of time. Average rates of nonadherence to treatments for chronic conditions are 50–60 percent. Adherence rates are variable. Higher rates of nonadherence occur for more complex treatment regimens and in populations with increased risk factors. But no chronic condition is "immune" from the impact of treatment nonadherence. Treatment nonadherence limits the effective or therapeutic dose of medical treatment and hence effectiveness, can contribute to therapeutic errors (for example, overdosing), and disrupts therapeutic alliance and relationship (for example, can trigger mutual frustration and mistrust). Treatment nonadherence affects morbidity of illness (for example, symptoms), drug resistance (for example, HIV infection), mortality, and increased health care use and costs of care. Good adherence to treatment for chronic physical and behavioral conditions is a very difficult task because medical treatments are time and energy consuming, burdensome, and sometimes aversive. Medical treatments must be repeated many times and require substantial support and reinforcement. Immediate benefits of treatment of chronic conditions are not always experienced.

Formulations present important but neglected barriers to adherence to medication treatment. Formulations are a prevalent barrier in multiple pediatric conditions, have a high salience for children, and have a negative impact on families. Improved formulations can promote adherence because they do not require patients and families to change behavior and do not add burden to physicians' clinical management. Research and clinical experience underscore the importance of formulations on pediatric treatment adherence. Formulation barriers to treatment adherence are identified in multiple studies across a range of conditions. Formulation barriers disrupt adherence and may affect clinical outcomes. Ingestion issues are primary factors in measures of perceived barriers to medication adherence for parents and adolescents.

Advances in improved drug formulations should improve adherence and health outcomes in clinically significant ways. There is an important opportunity to vary parameters of formulations in drug development and test the impact on adherence. Consumers—children, adolescents, and families—should be involved in formulations research. A range of valid methodologies are now available to assess and develop research examining treatment adherence and barriers to adherence.

Integrating Quality by Design (QbD) and Biopharmaceutics for Pediatric Drug Development

Arzu Selen, Ph.D., Associate Director, Biopharmaceutics, Office of New Drug Quality Assessment, Office of Pharmaceutical Science, CDER, FDA

QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Key considerations for drug quality (that is, patient benefit) are product, manufacturing process, and understanding the main sources of variability.

QbD can be applied to biopharmaceutics principles through product/process design and risk assessment and risk control. The impact of QbD will be greater patient benefit by enabling continuity (systems approach), leveraging information/knowledge (including better use of prior

information), using smart study designs and tools, and making better decisions (risk assessment and management).

Questions for biopharmaceutics risk assessment include:
- Is the dosage form suitable for the target patient population? How is it administered?
- How are bioavailability, integrity, and stability ensured?
- What should be the desired *in vivo* drug release characteristics and how can they be achieved?
- What are critical aspects of the formulation with respect to drug release including excipient choice and amount?
- Is the manufacturing process capable of consistently delivering the product attributes?

The differences and benefits of QbD implementation are timing and more choices, application of a systems approach, and broader and greater benefit. Application of QbD for drug development is getting established. Planning for pediatric drug development early on creates a window of opportunity by taking into account suitability of the process and product for pediatric patients and/or other special patient populations. Quality target product profile (QTPP) and biopharmaceutics risk assessment road map will identify critical factors, tools, and enablers and facilitate better decision-making. Sharing and leveraging critical considerations, tools, and enablers can support development of old and new drugs (including those that are off-patent).

Future considerations for QbD and biopharmaceutics are as follows:
- The dosage forms are age-appropriate or age-friendly for special populations or simple to adjust (that is, flexible).
- Products are optimized based on desired/target *in vivo* performance per QTPP.
- Development steps are played out first according to a risk assessment plan taking into account the desired outcome and all components. The risk assessment plan is optimized for effective linking of the process, product, and patient benefit. Issues are considered/addressed in a multidisciplinary/multidimensional approach. Knowledge is leveraged and made available for others to benefit multidisciplinary/multidimensional collaborations and knowledge sharing.
- Advance methodologies for predicting *in vivo* performance are developed.

Economic Issues for Making Available Adequate Drug Dosage Forms

Christopher-Paul Milne, D.V.M., M.P.H., J.D., Associate Director, Tufts Center for the Study of Drug Development, Tufts University

The development of adequate pediatric drug dosage forms is essentially a market problem. The elderly population (65 years of age and older) spends, on average, about 10 times more than the pediatric population (0–17 years of age) spends. Economic disincentives include a small market, high off-patent use, and fewer chronic illnesses among children. There are no incentives for generic drug makers. Formulation development requires 2 years, and the costs are high. Chemical manufacturing and control costs range from $8 million to $15 million to develop a typical pediatric formulation.

Pediatric formulation needs are numerous, varied, and complex. In March 2011, the FDA began removing certain unapproved prescription medicines intended to relieve cough, cold, and allergy symptoms and were concerned that some of the products were inappropriately labeled for use by infants and young children. Many of these unapproved drug products contained the same ingredients as the over-the-counter products previously subject to a 2008 FDA public health advisory. After reviewing almost 50,000 prescriptions for narcotics given to children up to age 3, researchers found that about 4 percent were given an overdose.

Some problems with pediatric formulations have recently been recognized. Children with certain conditions, such as autism, appear to have aversions to sweet foods or specific flavors. Spending on drugs for children in the United States rose 10.8 percent in 2009, nearly triple that of the general population, mostly due to obesity and diabetes but also due to asthma, hypertension, and hypercholesterolemia. Medicaid and third-party payer policies often do not favor reimbursement for pediatric formulations either because they are not making the state formularies or get listed as second- or third-tier drugs because there are already adult generics on the formulary.

Incentives offered by legislation such as the FDA Modernization Act, the BPCA, the Pediatric Research Equity Act (PREA), and the FDA Amendments Act have increased the number of drugs studied for pediatric indications. The PREA and the BPCA programs increased the number of studies focusing on off-label use and labeling changes for off-patent drugs. Since 2001, about 450 drugs have been labeled for pediatric use. The Prescription Drug User Fee Act, the Patient Protection and Affordable Care Act, and the European Medicines Agency (EMA) have also had an impact on pediatric drug formulations and devices.

Economic drivers of the U.S. pediatric drug market include increasing use of pediatric drugs to treat chronic conditions, the need for easy-to-swallow formulations, and the recognition of the importance of childhood well-being for healthy adulthood, and drug company market positioning. Changes in the world market (for example, increasing proportion of worldwide pediatric population and projected increases in chronic diseases) will also be an economic driver of pediatric drug formulations development.

Day 2

EU Advances in Pediatric Formulations

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The EU regulation "Medical Products for Paediatric Use" implemented the Pediatric Committee (PDCO) in the EMA. The PDCO advises pharmaceutical companies and supervises all Pediatric Investigation Plans (PIPs), which have to be submitted according to EU regulations. A PIP specifies the timing and the measures proposed to assess the quality, safety, and efficacy of the medicinal product in all subsets of the pediatric population that may be concerned. In addition, a PIP describes any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safe, or more effective for different subsets of the pediatric

population. For new chemical entities, a Supplementary Protection Certificate gives 6 months of market exclusivity and 24 months for orphan diseases. For "old" drug substances, the Paediatric Use Marketing Authorization gives drug companies 10 years of exclusivity of study results.

The EU PFI Consortium is composed of drug companies, associations, and academia. The purpose of the EU PFI is to

- Identify the issues and challenges associated with development of pediatric formulations in order to raise awareness and consider ways toward better medications and clinically relevant dosage forms for children
- Identify potential information, knowledge, and know-how gaps in the pediatric formulations development
- Promote early pharmaceutical consideration for development of pediatric medicines
- Improve the availability of information of pediatric formulations.

The goals of the EU PFI are as follows:

- Sharing experiences and expertise through interactive discussions between industry, academia, and clinical and regulatory professionals
- Making the information visible/available through publications and Web sites
- Raising awareness through publications and regular conferences/workshops
- Lobbying to generate funding to support future academic or industrial research worldwide
- Linking with other interested parties and relevant networks to maximize the operational capacity and information exchange.

There are five work streams in the EU PFI: pharmaceutical excipients, taste masking and testing, administrative devices, extemporaneous preparations and dispensing, and age appropriateness of formulations. Many studies have been conducted under these work streams. One example is a recent study of acceptability of and capability to swallow coated or uncoated mini-tablets compared with syrup in children 6 months to 6 years of age (n = 306). All three formulations were well tolerated. None of the children choked on either syrup or uncoated mini-tablets. Two of the 306 children (both in the 6–12 month age group) choked on the coated minitablet; however, the events were without clinical relevance. As part of the excipient work stream, an EU PFI/U.S. PFI collaboration is developing a database of safety and toxicity of pediatric excipients.

In conclusion, pediatric drug formulations are a key issue in European drug companies' research and development. Specific focus areas are safe excipients, age-appropriate dosage forms, taste masking and taste assessment, child-appropriate medical devices, extemporaneous compounding, and international approaches.

FDA/EMA Information Exchanges: Addressing Differences

Mary Dianne Murphy, M.D., F.A.A.P., Director, Office of Pediatric Therapeutics, Office of Special Medical Programs, Office of the Commissioner, FDA

The FDA/EMA information exchanges are important because governments are driving pediatric product development. Without legislative initiatives, it would not get done. Some of these initiatives provide financial incentives. It becomes incumbent on the various governments to

ensure that children are placed in trials that ask useful public health questions that will enhance the science of how the product is used for children. Legislative initiatives have led to 426 pediatric labeling changes.

The United States, since 1997, and the EU, since 2007, have created incentive and requirement programs for the development of therapeutics for the pediatric population. There are similarities and differences between the U.S. and EU pediatric legislations. The United States has two separate processes for the incentive (the BPCA) and requirement (the PREA) that are only partially unified, whereas the EU's pediatric process is unified under their legislation. Another difference is that the EU process is asking for information earlier in development. What is now evolving for the planning of pediatric development programs is more awareness of the need to integrate pediatric thinking earlier in overall drug development. This is being driven by the global pediatric regulations.

The international information exchange process among the FDA, the EMA, Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada (HC) are as follows:

- The EMA sends monthly list of PIPs.
- The FDA and the EMA identify products and general scientific issues for discussion.
- The EMA sends the summary reports, and the FDA develops a spreadsheet with data on pediatric trials for products to be discussed.
- Monthly teleconferences are held with the EMA, with participation by the PMDA and HC as observers.

Discussion topics have included information not shared by the drug development sponsor with the other agency, safety concerns, endpoint differences, indication differences, age differences, timing of initiation of pediatric studies, juvenile animal studies, and formulation issues. From August 2007 to August 2011, the FDA/EMA/PMDA/HC collaboration discussed 242 products; 158 of 242 product discussions included participation by the FDA review divisions. There were 25 non-product specific discussions of general topics. Some discussions focused on safety information not communicated by the drug development sponsor. The FDA/EMA/PMDA/HC collaboration provides a robust ethical and scientific framework for pediatric studies; identifies and addresses key science, safety, and ethics issues; and provides a forum for sharing critical information not shared by the drug development sponsor with one of the agencies (safety concerns, including clinical hold; ongoing or planned studies). Ongoing additional pediatric international initiatives include FDA and EMA personnel exchanges, working groups, and WHO initiatives.

In the United States, the FDA and the NIH have implemented a new pediatric formulations initiative. The FDA and the NIH collaborate on posting a public platform based on their compilation and analysis of all available data related to successful development of pediatric formulations that manufacturers can then apply to the development of new formulations of new and existing APIs. Platforms include drops, syrups, suspensions, sprinkles, capsules, chewable tablets, and oral disintegrating tablets. The FDA has developed a list of approximately 400 products that are commonly used in pediatrics (primarily for oral use) and has determined which ones have pediatric formulations. For products with pediatric formulations, the FDA/NIH

pediatric initiative is determining which technologies were used and how they were used to develop these formulations and which ones are publicly available. In addition, using prototypical drug products with pediatric formulations, the initiative is categorizing molecular structure, physiochemical and other characteristics (for example, aqueous solubility and intestinal permeability, pH, dissolution, taste, and heat stability), and excipients (type and concentration). Using this information, the FDA/NIH pediatric initiative will (1) determine the best formulations technology to produce ideal pediatric dosage forms for specific drug categories, (2) produce prototype batches of selected pediatric formulations, and (3) present the results in public forums (for example, publications, presentations, and on the FDA Web site).

In conclusion, pediatric trials are unique and often global. Pediatric legislation is driving global development. Global collaboration and information sharing is critical to ensure enrollment of children in scientifically and ethically sound trials that answer a needed question. The pediatric therapeutic knowledge gap is closing, but challenges and gaps remain. Collaboration is essential to address these challenges and gaps. Although differences will remain, resources can be maximized by sharing information.

Status Update on Extemporaneous Formulations

Loyd V. Allen, Jr., Ph.D., R.Ph., Editor-in-Chief, International Journal of Pharmaceutical Compounding

Compounding is the preparation, mixing, assembling, altering, packaging, and labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative based on relationships among practitioner, patient, pharmacist, and compounder in the course of professional practice. Compounding is any manipulation of a drug or drug product outside its official labeling. Compounding differs from manufacturing in the presence of the patient/physician/pharmacist relationship. The role of the compounding is to provide individualized medications. Compounding emphasizes quality, documentation, and testing.

The types of compounding pharmacies include independent, chain, hospital, mail-order, compounding-only, specialty, and nuclear. More than 70 percent of pharmacies report doing some compounding. Virtually all hospitals do compounding. It is estimated that 10 percent of all prescriptions and medication orders are compounded ($25–$30 billion dollars per year). Pharmaceutical compounding is growing and is a critical part of the health care system. Some of the reasons for the growth of pharmacy compounding include limited dosage forms, limited strengths, home health care, nonavailable drug products and combinations, orphan drugs, new therapeutic approaches, and special populations.

The USP 2010–2015 includes general chapters, monographs, USP laboratory-stability studies, and compounding for investigational and hazardous drugs. It is estimated that more than 10,000 different formulations (nonsterile and sterile) are compounded daily. Most have no long-term stability studies. They have short "beyond-use dates" and do not use "expiration dates."

There are 150 official USP compounded formulations, with 80 formulations in process. These formulations need stability studies done by validated laboratories. Stability is currently determined from peer-reviewed literature and contract laboratories. Developing USP monographs with stability studies is the fastest way to solve the pediatric formulations situation.

Growth in compounding pharmacies is expected to continue because discontinued drugs and drugs in short supply will need to be continued. Compounding will be needed for alternative drug delivery methods, dosing adjustment, short-dated (unstable) drugs, and drugs lacking pediatric formulations. Future trends in high-technology pharmacy compounding include the application of pharmacogenomics, new compounded drug delivery systems, and nanotechnologies.

Taste versus Flavor

Julie Mennella, Ph.D., Faculty Member, Monell Chemical Senses Center

Flavor is defined by taste, chemical irritation, and retronasal olfaction. The flavor involves each of these chemical senses. The basic biology of the chemical senses involves the domains of sensory perception, affect (that is, hedonic responses), and physiological consequences such as gagging and vomiting.

The five primary tastes are sweet, umami, sour, salty, and bitter. Sweet and umami have one receptor, whereas bitter has about 25 receptors—called T2Rs. Taste receptors are located in gustatory (oral) and nongustatory tissues, including the gut, brain, human airway smooth muscles, and reproductive tissues. There is a substantial degree of sequence diversity and variation in taste receptor genes. Of all the taste qualities, bitter is the most diverse among people. Taste plays its most important role during childhood.

Chemical irritations are sensations resulting from chemicals stimulating receptors and free nerve endings of the trigeminal and vagus nerves that lead to oral perceptions such as pain, heat, coolness, tingling, tickle, and itch. A family of transient receptor potential channels is involved in detecting many of these chemicals. Very little is known about ontogeny of this sense.

Most of flavor is odors perceived retronasally. Odors (chemicals) can reach the olfactory epithelium via the nose (orthonasal route) or mouth (retronasal route) and information is then sent to glomeruli in the olfactory bulb to mitral cells traveling to higher centers in the brain. Olfactory receptors are encoded by the largest gene family in mammalian genomes, with more than 900 genes.

Many active pharmaceutical ingredients taste bitter and irritate the oral cavity. The more potent the drug, the more bitter and/or irritating it will be. The more bitter and irritating its flavor, the more likely it will be rejected by children. There are two approaches to block or mask bitter taste: (1) pharmacological antagonism of bitter compound activation or transduction pathways (bitter blocking) and (2) psychological interference with bitterness perception (bitter masking), which is often accomplished with mixtures of tastes (sweeteners) and flavors (bubble gum).

One of the most widely studied individual differences is the genetically determined sensitivity to certain bitter tastes. From birth to old age, the ability to taste bitter compounds, such as phenylthiocarbamide and propylthiouracil, is evident in human populations. Person-to-person differences in the taste response to these bitter chemicals are largely determined by genetic variation in a bitter receptor gene known as the *TAS2R38* gene.

In a study of a racially and ethnically diverse sample of children, adolescents, and adults, alleles of the *TAS2R38* gene were genotyped for the three most common variant sites of the *TAS2R38* gene (A49P, V262A, I296V), Taste sensitivity to polythiouracil was assessed by using forced-choice procedures, embedded in the context of games, that were sensitive to the cognitive limitations of pediatric populations. The results showed that the phenotype-genotype relationship was modified by age. Genetic variation in bitter sensitivity may account for differences in medication compliance among children.

In adults, sodium salts can suppress the bitter taste of many bitter compounds, presumably by acting at the peripheral taste level. In a study of children, sodium suppressed the bitter taste of urea and caffeine. Salts may be effective bitter suppressors for some bitters (not all) because salty tastes are preferred by children.

In conclusion, "bad taste" is going to be an ongoing pediatric drug formulations problem because of the diverse number of receptors, the multiple transduction pathways, and age-related sensitivity based on genotype. Infants and children live in different sensory worlds, and there is a need for validation of taste assessment methods. Although there are no easy solutions, children's acceptance of many medicines can be improved by applying knowledge gleaned from basic and applied research in the chemical senses.

PFI Working Groups: Where We Are and What Needs to Be Done?

Four PFI working groups held concurrent breakout sessions to discuss an issues analyses framework to capture known information and identify gaps; key issues and their translation into short-, mid-, and long-term goals; and action plans and deliverables to implement the goals. The working groups' summaries are as follows:

Biopharmaceutics Working Group. *Co-chairs: Dr. Suryanarayanan and Alan Parr, Ph.D., Pharm.D., Director, Department of Biopharmaceutics, Glaxo Smith Kline*

The working group discussed four broad issues for implementation: excipients, pediatric formulations development, platform development, and taste masking.

- **Excipients.** Although there is anecdotal evidence, it is not known whether there is a systematic problem with excipient use in pediatric formulations development and whether the problem is more relevant to certain age groups, such as neonates. One approach to address these issues would be to identify a small number of excipients that are safe for the pediatric population, which would serve as a starting point for formulation development on a larger scale. A pharmaceutical excipient database would help identify these excipients.

Although there is evidence of adverse events (AEs) linked to excipients, the reporting has not been systematized. AEs associated with specific excipients should be validated. A next step would be EU-U.S. collaboration to develop a database to help identify those excipients that could be problematic.

- **Pediatric Formulations Development.** The first step in pediatric formulation development is the transfer of technology from adult formulations, which is easiest to do with solution dosage forms. Developing solid dosage forms will be more challenging. Given the limited pediatric population and the costs, formulations with broad applicability should be considered. Broadly applicable formulations should be able to be used across a wide dose range. Formulation development should be harmonized across international regulatory bodies. One possible source of financial support is WHO and could be leveraged with other organizations. An American Association of Pharmaceutical Scientists (AAPS) Pediatric Task Force could provide the initiative for collaboration among the pediatric formulation community. Effective multi-particulate systems provide an example of successful development of pediatric-appropriate dosage forms.

- **Platform Development.** Developing platforms that can work across scales and patient populations would facilitate formulation development with limited resources. Pharmaceutical companies are interested in developing platform technologies for adult formulations. The challenges, limitations and the potential utility of these platforms will become available to the broader scientific community (while retaining proprietary information). Knowledge of the challenges of platform development for adult formulation could be applied to pediatric dosage forms. Forming a consortium for platform development would be a logical first step, which would minimize expenses and allow sharing knowledge across the scientific community.

- **Taste Masking.** Universally acceptable taste-masking technology does not seem to exist. Aversion to bitter taste is universal. Many current taste masking efforts are directed at reducing the negative attributes of pediatric dosage forms, which is a big challenge.

- **General Comments.** Data mining will help to learn about research done so far and may provide information on past mistakes. Whether data submitted to the FDA can be mined, while ensuring that anonymity is maintained, needs to be determined. Developmental (failed) efforts in pharmaceutical companies may be useful in pediatric formulation development. Developing predictive tools and capabilities will be a long-term project. The challenge is to build a knowledge base with predictive capabilities for solubility, stability, taste, toxicity, and the concept of a virtual patient. Linking computational tools to the appropriate expertise may provide great benefits. The goal of predictive capabilities is to reduce experimental work. Funding for pediatric formulation development is a major challenge. The NIH has consistently stated that pediatric formulation development should be funded by industry. The importance of drug delivery is not recognized in the pharmaceutical community. Another challenge is training the next generation of scientists with expertise in formulation development. Pediatric formulation development requires information sharing and collaboration among industry, government, and academia.

In a question-and-answer session the following topics and issues were discussed:

- Forming a new working group to focus solely on taste masking
- A drug industry platform or platform technologies for developing the best taste masking and delivery PK profile
- FDA data mining experiences and challenges
- Learning from pediatric drug development "mistakes"
- Types of data sought from data mining (for example, AEs linked to specific excipients and certain age groups; with more than one type of dosage form or delivery for a drug, why one worked and the other did not)
- The need for collaboration among the working groups for taste masking
- FDA guidance on bioavailability expectations for new or innovative pediatric products.

Taste and Flavor Testing Working Group. *Co-chairs: Dr. Mennella and Jeff Worthington*

The working group developed an issues analysis document that identified about 110 questions to address data gaps and research initiatives. The NIH and other agencies should develop a technology pathway or plan to answer questions with regard to taste receptors, perception, consequences, and hedonics, as well as taste masking. The working group narrowed the questions to five major areas:

- Global regulatory requirements
- Preclinical taste assessment tools
- Clinical taste assessment tools
- Age-related changes/culture
- Taste masking technology.

The working group discussed global regulatory requirements and guidance on acceptability when conducting pediatric palatability studies and decided that it should not address excipients and age-appropriateness of oral dosage forms. Preclinical and clinical taste assessment tools were combined into one area. The working group recommended that a new working group for taste masking technology be formed.

The working group listed prioritized next actions:

- Develop open source methods for measuring palatability at various ages; development phases are (1) preclinical tools that can be used in animal or *in vitro* models to predict bitterness or other aversive attributes prior to human studies, (2) identifying tools and techniques to guide development of palatable formulations, and (3) tools and methods to measure palatability or acceptability in patients in a clinical setting.
- Collaboration among industry, government, academia, and nonprofits to develop methods that could ultimately be used for regulatory guidance
- Validation of tools and methods.

BCS Working Group. *Chair: Dr. Amidon*

The working group agreed to establish a list of pediatric drugs for which there are indications or labeling, classify those drugs, and evaluate the 50 most used drugs in pediatrics. The drugs will be classified for absorption, intestinal lumen brush border metabolism, metabolizing enzymes that affect absorption, and hepatic first-pass metabolizing enzymes that limit systemic availability. Most of this information is probably not available. 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. Simulation studies will be conducted for amoxicillin and possibly valganciclovir. Metabolism information sources will be *in vitro* and *in vivo* studies. Pediatric information of interest includes GI volume, enzyme differentiation, and transporter maturation—particularly identifying information related to carrier-mediated drugs. Taste masking may eventually be included—for example, whether taste masking alters the bioavailability of BCS Class 1 and Class 3 drugs. Taste masking information on BCS Class 3 drugs may be more important.

New Technology and Drug Delivery Systems Working Group. *Co-chairs: Michael Baltezor, Ph.D., Director, Biotechnology Innovation and Optimization Center (BIO Center), Deputy Director, Institute for Advancing Medical Innovation, University of Kansas; and Karen C. Thompson, Ph.D., Senior Investigator, Pharmaceutical Research, Merck Laboratories*

The working group discussed and prioritized the following topics and issues:

- Inhalation products and the need for working with the International Society for Aerosols in Medicine (ISAM) to develop anatomical models for breathing of different pediatric patient age groups
- Working with ISAM to assess existing anatomical models and propose new models to assist product design
- Testing inhalation devices and spacers with regard to appropriate dosing
- Transdermal product gaps (as of 2009, there were 2 for pediatric use and 19 for adults)
- Dose adjustment issues with transdermal products
- Availability of pediatric tissues from the National Disease Research Interchange for studies
- Development of new chemical entities, specifically dendrimers
- Need for better guidance and specificity on controls for dendrimers manufacturers
- Identifying appropriate dendrimer testing for pediatric animal models
- Need for flexible dose-adjustable devices for mini-tablets and granule formulations
- Staying informed about newly patented dose-adjustable devices.

General Discussion Session

The following topics and issues were discussed:

- The lack of industry incentives to promote pediatric applications
- Collaboration among industry, academia, and government to develop pediatric formulations and cure childhood diseases
- Funding mechanisms to establish pediatric tissue banks for *in vitro* testing
- Sources of and access to pediatric tissues for tissue banking

- Limited amounts of quality pediatric tissues
- Bold initiatives to address the unmet needs of pediatric formulations development (for example, establishing innovative, dedicated, pediatric-focused drug companies)
- AAPS Pediatric Task Force efforts to establish an efficient development process for pediatric formulations and biopharmaceutics
- Commercialization of pediatric formulations with high unmet needs
- Viability of compounding pharmaceuticals
- Use of different formulations in different clinical trials and lack of description of the formulations
- Global issues of compounding; impact of U.S. decisions on other countries.

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