Editorial

Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatrics Formulation Initiative: Proceedings from the Second Workshop on Pediatric Formulations

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ABSTRACT

Background: The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development of the National Institutes of Health (NIH) organized a workshop held in November 2011 to address knowledge gaps that limit the availability of adequate pediatric formulations. This workshop was used as a means to identify the types of research innovations needed and to stimulate research efforts designed to improve the availability of pediatric formulations and the technologies required to make these formulations.

Methods: Information for this article was gathered from the proceedings of the Second US PFI Workshop sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development in Bethesda, Maryland, on November 1 and 2, 2011, as well as from post-workshop discussions. The workshop preparation began with formation of 4 working groups: Biopharmaceutics, Biopharmaceutics Classification System (BCS), New Technology and Drug Delivery Systems, and Taste and Flavor.

Results: The recommendations of the 4 working groups will form the basis for the development of a blueprint to guide future research efforts. The pediatric-specific problems identified include the heterogeneity of the population, the small size of the pediatric drug market, the limited number of new formulations for the large number of off-patent and unlabeled drugs, and the lack of universal agreement on how to define appropriate formulations for different ages and stages of development. There was consensus on the need to develop a universal technology platform for flexible pediatric dosage forms, transforming an empirical process into a science-based platform. A number of problems affect the availability of drugs in the developing world. Age-appropriate solid oral pediatric medicines for common diseases can have a global impact. Success on a global scale depends on the commitment of policy makers, regulators, scientists, pharmaceutical companies, sponsors, government, and research foundations to address gaps in knowledge and solve public health issues related to the availability of formulations in the developing world.

Conclusions: Solutions to the worldwide lack of appropriate pediatric formulations will require the development of a road map and the commitment of policy makers, regulators, scientists, pharmaceutical sponsors, academic institutions, governments, and research foundations. The development of a universal, cost-effective platform using existing or developing innovative technology that produces flexible pediatric dosage forms remains an important but elusive goal. (*Clin Ther.* 2012;34: S1–S10) Published by Elsevier HS Journals, Inc.

Key words: pediatric formulations, drug delivery systems, novel formulations.

INTRODUCTION

The NICHD organized a workshop held in November 2011 to address knowledge gaps that limit the avail-

Publication of this supplement was supported by The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH).

Accepted for publication October 4, 2012.
http://dx.doi.org/10.1016/j.clinthera.2012.09.013
0149-2918/$ - see front matter

Published by Elsevier HS Journals, Inc.

ability of adequate pediatric formulations. The workshop is part of the US Pediatric Formulations Initiative (US PFI). The US PFI was established in 2005 to address the lack of appropriate formulations in children in response to the Best Pharmaceuticals for Children Act (BPCA).[1,2] This workshop was used as a means to identify the types of research innovations needed and to stimulate research efforts designed to improve the availability of pediatric formulations and the technologies required to make these formulations. The overall goal of the US PFI was to develop a blueprint to identify the types of research innovations needed and to uncover knowledge gaps and stimulate research. The BPCA legislation was enacted in 2002 and reauthorized in 2007 and 2012. 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 study. Under Section 409I of the legislation, several factors are listed as areas of consideration in prioritizing drugs, including the need for reformulation of a drug (Public Law 107-109; January 4, 2002). The BPCA of 2007 and 2012 continued the mandate of prioritizing therapeutic gaps and publishing that list every 3 years. Lack of pediatric formulations remains a significant problem in delivery of appropriate therapeutics; the NIH is therefore committed to identifying research needs in this area. The November 2011 workshop preparation began with formation of 4 working groups: Biopharmaceutics, Biopharmaceutics Classification System (BCS), New Technology and Drug Delivery Systems, and Taste and Flavor. These groups began the process of identifying issues, gathering needed information, and considering possible ways to overcome barriers to the development of pediatric drug formulations.

OVERALL GOAL OF THE US PEDIATRIC FORMULATION INITIATIVE

The overall goal of the US Pediatric Formulation Initiative (US PFI) is to develop a blueprint to address issues related to pediatric formulations needs, including gaps in knowledge; determination of the types of research innovations needed; and proposed solutions to the identified problems. The blueprint will serve as a guide for future interactions (both national and international), potential development of research initiatives and programs, and identification of funding needs and resources. 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.

2011 US PFI WORKSHOP OBJECTIVES

The purpose of the 2011 PFI workshop was to review a range of topics concerning challenges to creating pediatric formulations, as well as to discuss the current gaps in knowledge and technological advances. The specific objectives were to summarize current knowledge, develop new approaches that address challenges, and identify cutting-edge formulation technologies used in adults that have applicability in children. The workshop participants reviewed the work of the individual PFI working groups, added new items, prioritized the topics, and discussed ways to stimulate further research in the field.

WORKING GROUPS OF THE US PFI WORKSHOP

The working groups included representatives from academia, the pharmaceutical industry, and government agencies, including the National Institutes of Health and its centers and the US Food and Drug Administration (FDA). These groups began the process of identifying issues, gathering needed information, and considering possible ways to overcome barriers to the development of pediatric drug formulations.

The working groups met initially by teleconference during the summer and fall of 2005. The groups met face to face for a working meeting December 6 and 7, 2005, in Bethesda, Maryland, and have continued to communicate electronically since that time. A summary of the PFI activities related to the 2005 workshop has been published elsewhere.[3,4]

In the 2011 PFI workshop, the 4 working groups were asked to develop and prioritize short-, mid-, and long-term goals.

Biopharmaceutics Working Group

This working group reviewed new approaches to pediatric formulations development by transforming an empirical process into a scientifically based platform, identified taste-masking technologies appropriate for children, and evaluated new concepts in pediatric formulations design.

Biopharmaceutics Classification System Working Group

This working group focused on the development of a framework designed to close the knowledge gap on the effects of developmental changes on drug disposition for

selected Biopharmaceutics Drug Disposition Classification System (BDDCS)/Biopharmaceutics Classification System (BCS) class 1 through 4 drugs in pediatrics. A major goal of the working group was to identify methods to validate the use of the BCS and the BDDCS in children.

New Technology and Drug Delivery Systems Working Group

This working group discussed the means to stimulate the development or application of new methods of drug delivery for children, the adaptation of new technologies (eg, nanotechnology) for use in children, and the development of pediatric-specific devices.

Taste and Flavor Working Group

This working group summarized current knowledge of drug palatability and methods used to promote the development and/or harmonization of age-appropriate, standardized, psychophysical methods for testing drug formulations in child- and adult-testing panels; proposed the development of in vitro and animal models to predict the degree of bitterness likely to be sensed by children; and suggested research designed to increase understanding of the intracellular mechanisms of bitter taste signaling.

WORKING GROUP SUMMARIES

The 4 PFI working groups held concurrent breakout sessions and were asked to: (1) develop an issues analysis/summary document to capture known information and identify gaps; (2) identify and prioritize the key issues and their translation into short-, mid-, and long-term goals; and (3) develop an action plan and deliverables to implement the goals. The summaries of the working groups are discussed in the following sections.

Biopharmaceutics Working Group

The working group discussed 7 broad issues for implementation: safety and choice of excipients, pediatric formulations development, platform development, taste masking, use of computational tools, nanotechnology, and a global platform.

Excipients

Information on well-known excipients is available (eg, monographs and the FDA's inactive ingredients database to select appropriate excipients). For new excipients, a battery of FDA-approved tests is required. There are challenges in selecting pediatric excipients (eg, there is no pediatric inactive ingredients guide list). One of the challenges to extemporaneous compounding of drugs is the composition of liquid compounding vehicles. Pharmacy practice guidelines list excipients that should not be used in liquid formations, yet some compounding vehicles contain banned excipients (eg, propylparaben). The choice of excipients and their associated toxicities need to be justified before inclusion.

Although there is anecdotal evidence, it is not known whether there is any systematic safety problem with excipients currently used in pediatric formulations or whether safety concerns might be more relevant to a specific age group such as neonates.[5] One approach to addressing these concerns would be to identify excipients frequently used in pediatrics and to evaluate evidence of toxicity, based on reports to the FDA and a literature search. A pharmaceutical excipient database would help identify toxicities identified or reported in experimental animal and human subjects. This type of knowledge base can identify the types of studies needed to validate purported excipient toxicity. Collaborations with the European Union PFI and the US PFI have led to the development of a database to help identify those excipients that could be problematic, based on experimental, in vitro, and/or human data.[6]

Pediatric Formulations Development

The first step in pediatric formulations development is the transfer and application of technology from adult formulations. Formulations with broad applicability that could be used for a wide range of doses should be considered. Formulations development could be harmonized across international regulatory bodies. One possible source of financial support is from the creation of private–public partnerships that include pharmaceutical sponsors, major foundations, and governmental policy makers. The World Health Organization could provide the leadership necessary to convene meetings of major stakeholders to address formulation needs in underdeveloped countries. The World Health Organization strategy for improving medication adherence calls for "convenient and simplified dosing regimens and appropriate and palatable formulations."[7] An American Association of Pharmaceutical Scientists Pediatric Task Force could provide the initiative for collaboration within the pediatric formulation community.

Platform Development

For oral medicines requiring precise dosage measurement, the most suitable dosage form should be

based on use of a solid platform technology (eg, a multiparticulate solid) with tailored dosage strengths and dosage forms.

Addressing short-term needs requires the innovative application of existing technology rather than the introduction of innovative technology. 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 all active pharmaceutical ingredients (APIs).[8] Flexible, simple dosage forms based on multiparticulates (eg, granules, pellets) can be developed. Basic forms or secondary processing into a range of solid dosage forms provides dose flexibility. Multiparticulate systems can be applied to fixed-dose drug combinations as well as variable ratio drug combinations.

Pharmaceutical companies are interested in developing platform technologies for adult formulations. Knowledge gained about the potential utility and limitations of these platforms could be shared with the broader scientific community (while retaining proprietary information). Identification 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. Such a consortium could minimize expenses and allow the sharing of knowledge throughout the scientific community.

Taste Masking

A universally accepted taste-masking technology does not exist. Aversion to bitter taste is universal. Many current taste-masking efforts are directed at reducing the negative attributes of pediatric dosage forms. Strategies to taste mask liquid dose forms include: (1) complexation and the use of sweeteners and flavors for solutions/syrups; and (2) salt forms, coatings, sweeteners, flavors, and viscosity builders for suspensions.

Computational Tools

Data mining for toxic reactions and adverse effects will help to determine what research has been done so far and may provide information on past omissions. It remains to be determined whether data submitted to the FDA can be mined in a way which ensures that anonymity is maintained. Development of predictive tools for valid extrapolation is a long-term goal. The challenge is to build a knowledge base that has the ability to reliably predict solubility, stability, taste, and toxicity to reduce experimental work.

Nanotechnology in Pediatric Formulations

The application of nanotechnology in drug development is rapidly evolving.[9] Nanoparticles are beginning to be considered for pediatric drug formulations, to increase the solubility of lipophilic APIs, and for drug targeting at the cellular and molecular levels. Potential advantages of this technology include improved targeting of drugs for delivery to specific tissues of interest, potential for controlled release of drug, and increased solubility of highly lipophilic/hydrophobic therapeutic agents. In addition, nanoparticles are being used for nanoimaging, therapeutics, and combinations therein such as "theranostics."

Some major disadvantages and concerns include: (1) nanoparticles <100 μm exhibit enhanced intrinsic cellular permeability properties and retention and can lead to toxicity at lower doses; (2) the need for the nanocarrier material to be biomimetic/biocompatible/biodegradable to reduce toxicity from the carrier; and (3) formulation stability issues because interface interactions are enhanced in nanoparticulate delivery systems.

Global Platform

It was recognized that since most children live in the underdeveloped world, the development of a platform on a global scale that utilizes solid dosage forms to avoid problems related to lack of refrigeration and water contamination is of paramount importance. Other factors include the need to provide flexibility in dosing options and take into account "end users" specifications. Economic consideration dictates the need to address national and regional manufacture limitations.

Recommendations

The Biopharmaceutics Working Group reached consensus on the need for a change of paradigm from an empirical to a scientific approach in the development of pediatric formulations. A materials science approach could be used to overcome solubility limits of pediatric drugs, increase bioavailability, decrease excipient exposure, and provide effective taste masking. This approach entails the use of modeling and computational analysis of drug molecules and application of chemometric analysis to predict solubility, stability, and taste.

BCS Working Group

The BCS[10] 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 3 ma-

jor 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; class 2 drugs have low solubility and high permeability; class 3 drugs have high solubility and low permeability; and class 4 drugs have low solubility and low permeability. The selection of excipients to maximize solubility and permeability depends on the BCS classification of the drug. The BCS has proven to be an asset to the FDA by creating a framework by which waivers of in vivo bioequivalence studies for suitable class 1 compounds can be approved. Drug development strategies can be determined by BCS classification.

The full predictive value of the BCS classification system may be realized and facilitated by the BDDCS.[11] This system allows for concurrent consideration of the absorption/transport/elimination interplay, thereby extending predictive application to food effects (specifically, high-fat meals).

The usefulness and applicability of BCS and BDDCS have not been studied for pediatric formulations. Differences in gastrointestinal tract physiology in children compared with adults make it likely that BCS and BDDCS will need to be updated for pediatric use.

The BCS group was convened to determine whether an analogous pediatric classification should be developed. The article by Abdel-Rahman et al in this issue describes in detail the activities of the BCS group.

Issues Identified by the BCS Working Group

The following biopharmaceutical issues were discussed:

- The challenges for studies of bioequivalence and bioavailability, as well as the correlation between in vitro and in vivo dissolution studies in adults, and extrapolation of these results to children
- The need to develop better predictive capabilities for new chemical entities
- The use of bioavailability for new chemical entities
- The use of bioequivalence for currently marketed products
- The lack of knowledge of pediatric gastrointestinal tract physiology
- Patient-to-patient variability within pediatric populations over an age spectrum
- Patient characteristics, disease state, and pharmacogenomics

Recommendations

For future discussions, the BCS group will be divided into 2 functional subgroups; 1 will deal with issues related to specific BCS classes of drugs used in pediatrics, and the other with absorption, distribution, metabolism, and excretion characteristics in children and specific areas requiring further research.

New Technology and Drug Delivery Systems Working Group

Topical Drug Administration

The clinical utility of topical drug administration is critically dependent on identifying improved delivery systems that will allow for the administration of therapeutic agents that have limited oral bioavailability. Within this context, amphiphilic, biodegradable polymers that can self-assemble into nanosized structures have been identified as a promising platform to develop cutaneous delivery carriers. Drug delivery systems developed for the adult population may not necessarily be suitable for the heterogeneous pediatric population, and the development of systems for use in children has been long neglected. New drug delivery systems that meet the specific pediatric requirements are needed.[12]

Novel techniques to enhance drug delivery through the skin are currently being investigated and include use of microemulsions and nanoemulsions; nanotubes; microneedles; iontophoresis; ultrasound; and increasing local skin temperature.[13] The use of the transdermal route for systemic delivery of a wide range of drug molecules in pediatrics has been experimentally tested, including peptide/protein molecules and genetic material. The use of microneedle arrays has been proposed as a method to temporarily disrupt the barrier function of the skin and to allow for the cutaneous absorption of macromolecules.[14]

Ocular Administration of Drugs

Ocular drug delivery remains challenging because of the complex structure of the eye. Commonly used formulations and drug delivery systems, such as eye drops and ointments, are inefficient, whereas systemic administration that results in adequate ocular concentrations requires high doses resulting in potentially significant systemic toxicity. There is an urgent need for more efficient, safer, and targeted ocular drug delivery and formulations.[15] Moreover, most of the ocular drugs approved for adult use have not been properly studied in newborns and children.

Development of drug formulations effective for delivery to the posterior eye in newborns and children to treat a number of ophthalmic conditions is emerging as a major challenge, due to the unique anatomy and physiology of the eye superimposed on dynamic and rapid developmental and maturational events. Intravitreal bevacizumab monotherapy, compared with conventional laser therapy, is currently being studied in infants with stage 3+ retinopathy of prematurity. No pharmacokinetic, pharmacodynamic, or long-term safety and visual outcome studies are available at this time.[16]

The use of ocular drug formulations in conjunction with noninvasive delivery-enhancing techniques such as ultrasound and iontophoresis could improve ocular drug delivery effectiveness. These formulations and techniques should be studied in newborns, children, and adolescents to establish tolerability and maximum efficacy of these agents for the treatment of ocular diseases in the developing eye. The major concern is that frequent administration of drugs using these methods can lead to retinal detachment, endophthalmitis, and increased intraocular pressure.[17]

Delivery of Inhaled Drugs for Children

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 of devices may simply not provide benefit or result in lack of use. 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 the patients and their ability to cooperate and tolerate therapy.

Determining the aerosol dose for infants is important. However, attempts to adjust the dose simply according to weight do not stand up to scrutiny. Infant and pediatric doses also differ from those in adults. Dose adjustments are currently largely based on opinion versus evidence. Children aged <3 years may not reliably use a mouthpiece; therefore, masks have been the primary alternative for infants and small children. Studies suggest that clinical efficacy is similar for aerosol delivery with both face mask and mouthpiece.[18,19] Masks are often used to adapt aerosol devices designed for adults for use in infants. Consideration must be given, however, to the marked differences in the anatomy and function of the upper airways in early childhood compared to adults.

Aerosol therapy in infants and small children can be improved. Areas for potential improvement include new devices that are appropriate across the range of pediatric patient ages and sizes, effective interfaces designed for use with all ages and sizes, improved uniformity and standards for in vitro testing, and rational guidelines for demonstrating efficacy and safety in the smallest of patients. Proper device selection and a good interface between aerosol generator and patients can greatly improve not only the effectiveness of therapy but the willingness of infants, children, and parents to continue therapy.

Pharmaceutical nanoparticle dosage forms have failed to overcome the problems associated with traditional inhalation therapy. Because of their submicrometer size, they can reach the distal airways and be more effective than conventional aerosol delivery for the treatment of local and systemic infections. Nanoparticles currently being tested, however, have poor pulmonary deposition efficiency.[20] The article by Fink in this supplement discusses the aerosol delivery devices currently available, their limitations, and the areas of research that need to be addressed in the future.

New Technologies Applicable to the Development of Pediatric Formulations

The tremendous progress that has been made by capitalizing on the genomic and proteomic revolution to engineer new therapeutic molecules has resulted in a very limited number of strategies to effectively deliver these molecules to therapeutic targets. Application of dendrimer-based nanotechnology has resulted in advances in the area of targeted cancer and imaging therapy. Dendrimers are tree-like, multifunctional, single-molecule, nanostructured polymers (~5–10 nm).[21] They have both molecular and nanostructural features. They are biocompatible, noncytotoxic, and cleared intact from the circulation. Specific dendrimers of interest include hydroxy-terminated generation-4 poly (amido amine) "neutral" dendrimers, with β-alanine repeat units (peptide-like). Their amide-amine-hydroxy structure is desirable for intracellular pharmaceutics. There are a variety of functional units on the molecule's surface to which drugs, targeting ligands, and imaging agents can all be attached at the same time.[22] The structural and functional aspects of den-

drimers have led to improved targeted therapeutic outcomes in cerebral palsy and retinal degeneration.[23]

Remote triggering devices are currently being tested to obtain precise control of the timing and duration of drug delivery and to improve efficacy.[24] The article by Timko and Kohane in this supplement summarizes this technology and some possible applications in pediatrics.

Recommendations

The working group recommended the following:

- Inhalation products
  - Working with the International Society for Aerosols in Medicine to assess existing anatomic and breathing models and to propose new models for different pediatric age groups that can be used to assist in effective product designs
  - Testing inhalation devices and spacers in pediatric subpopulations with regard to appropriate pediatric dosing
- Transdermal products:
  - Identifying the factors responsible for the paucity of pediatric products (as of 2009, there were 2 for pediatric use and 19 for adults)
  - Addressing dose adjustment issues with transdermal products
- Determining the availability of pediatric tissues from the National Disease Research Interchange for developmental pharmacology studies
- Dendrimers
  - Developing new chemical entities, specifically dendrimers
  - Obtaining better guidance on and specificity of controls for manufacturers of dendrimers
  - Identifying appropriate animal models to test dendrimers for pediatric products
- Developing flexible, dose-adjustable devices for minitablets and granule formulations

Taste and Flavor Working Group

The working group developed an issues analysis document that identified ~110 questions to address data gaps and potential research initiatives. One of the main recommendations was that the National Institutes of Health and other agencies develop a technology pathway or plan to answer questions with regard to taste receptors, perception, consequences, and hedonics/sensory preferences, as well as taste masking. The working group narrowed the questions to 5 major areas: global regulatory requirements; preclinical taste assessment tools; clinical taste assessment tools; age-related changes and culture; and taste-masking technology.

The working group recommended that a new working group for taste-masking technology be formed.

Research Considerations

Further understanding of taste and taste preferences in all pediatric age groups, taking ethnic and regional variations into account, is needed to provide optimal oral dosage forms. Because of regulatory issues, most medicines developed in laboratories cannot be tasted until the first clinical trials. Often, it is at this point that their unpleasant chemosensory properties are discovered, with many medicines perceived as bitter or even intensely bitter, which creates a roadblock for oral formulations aimed at children. Although these issues are of particular concern for children, it should be noted that many drugs taken by adults in capsule or tablet form present with secondary bitter, unpleasant tastes that likely occur as the drug circulates in the bloodstream and is thereby transmitted to the taste receptors, leading to patient complaints.

Recommendations

The Taste and Flavor Working Group identified several gaps in knowledge:

1. There is a need to develop age-appropriate standardized psychophysical methods for testing drug formulations in child and adult panels, and to validate these psychophysical methods. Attention to differences in taste ability among individuals and across age groups is needed.
2. Adult sensory panels are often used to determine palatability of pediatric formulations. Thus, there is a need to determine what types of adult sensory panels and psychophysical methods are most appropriate for predicting acceptance/compliance in the pediatric population.
3. There is a need to study the role of different textures, granularity, and smell of dosage forms in the acceptability of pediatric formulations.
4. During preclinical testing of a drug, sensory tests using animal models should be developed to predict the degree of bitterness likely to be sensed by human children and the efficacy of potential bitter blockers. The data obtained from animal models should be compared with data obtained

from artificial sensors as well as more traditional sensory analysis methods in current use.

5. Electronic tongues (artificial sensors also known as "e-tongues") should be developed and refined to screen new drugs for bitterness and bitterness blockers. Studies are needed to evaluate the value of electronic tongues to quantify bitterness and taste-masking efficiency in the development of pediatric formulations.[25]
6. Research aimed at increasing understanding of the intracellular mechanisms of bitter signaling should be expanded and exploited to assist in discovery of novel bitterness blockers that work in safe and effective ways and to characterize the developmental variations in these mechanisms.[26,27]
7. Research that explores the relationships between taste sensitivity and noncompliance in children should incorporate environmental and family support as cofactors.
8. A partnership between academics, government, and industry could be developed to gain access to existing yet proprietary data on taste masking, bitter and irritant blocking, and drug palatability. This effort would help to determine what approaches have been successful and what the major obstacles are with respect to drug palatability for pediatric populations.

CONCLUSIONS: THE FUTURE OF PEDIATRIC FORMULATIONS

The passage of legislation, both in the United States and in Europe,[28] and regulations to create incentives to stimulate the availability of adequate pediatric formulations have resulted in a modest increase in the number of new pediatric formulations. Unfortunately, the legislation is most applicable to new drugs. There are a large number of off-patent drugs for which no adequate pediatric formulations are available.

In the United States between August 1997 and July 2012, only 31 label changes have been made through the development of pediatric formulations of off-patent drugs. Although economic factors (eg, small pediatric market) are important determinants of the willingness of pharmaceutical companies to develop pediatric-appropriate dosage forms, application of newer technologies could substantially reduce the cost to develop a new formulation and will likely result in an increase in the availability of appropriate pediatric dosage forms.

A major future goal is to effect a paradigm change from trial and error to a scientific approach in the development of pediatric formulations. There is an urgent need to test flexible pediatric dosage forms (eg, minitablets,[29] orally dissolvable strips, dissolvable minitablets[30]) that are appropriate for a number of different pediatric subpopulations.

The development of a universal technology platform for flexible pediatric dosage forms, transforming an empirical process into a science-based platform, would constitute a major advance. This platform must be cost-effective and based on API molecular properties. It must support the development of systematic formulations methods to improve solubility and bioavailability and to mask taste. Pediatric formulations drug development programs can benefit from computational and data modeling in areas such as prediction of the taste of a drug and in silico design of novel taste inhibitors.

Future taste research should include research on the mediators of bitter taste and study of taste blockers, as well as newer methods for taste-testing in pediatrics. Incorporation of taste-related studies in clinical drug trials to systematically evaluate taste as well as parental perceptions and biases is highly desirable. There is also a need to test new drug delivery systems in pediatrics, as targeted therapeutic agents using nanoparticle-facilitated delivery are now being studied in adults. Targeted therapy using anticancer agents and anti-infectives encapsulated in nanoparticles holds considerable promise to reduce toxicity and improve the efficacy of drugs given to children. The rapid advances in peptide and protein pharmacology have fueled great interest in these compounds. Although initial attempts have failed, novel smart polymer-based drug delivery systems have been developed to deliver drugs at a controlled rate over long periods of time. This type of system will have significant pediatric applications.

A number of problems affect the availability of drugs in the developing world. Age-appropriate solid oral pediatric medicines for common diseases can have a global impact. A major challenge for the future is the training of the next generation of scientists with expertise in formulation development. Pediatric formulations development requires an interdisciplinary approach, information sharing, and collaboration among industry, government, and academia. Success on a global scale hinges on an alignment of vision and commitment of policy makers, regulators, scientists, pharmaceutical companies, sponsors, government, and research foundations.

ACKNOWLEDGEMENTS

The authors and the NICHD wish to recognize the intellectual contribution, dedication and efforts of members of the different working groups of the US PFI. All authors have made substantial contributions to the conception of the study, acquisition of the data, revising the study critically for important intellectual content, final approval of the version to be submitted.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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