# INSTITUTE OF MEDICINE

OF THE NATIONAL ACADEMIES

Forum on Drug Discovery, Development, and Translation

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# NICHD BPCA Program

## Pediatric Formulations Initiative

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NICHD/NIH

## NICHD BPCA related activities exclusive of off-patent drugs clinical trials

- Preclinical studies
- Determination of frequencies of conditions and of the use of off-patent drugs
- Newborn initiative
- Pediatric formulations initiative

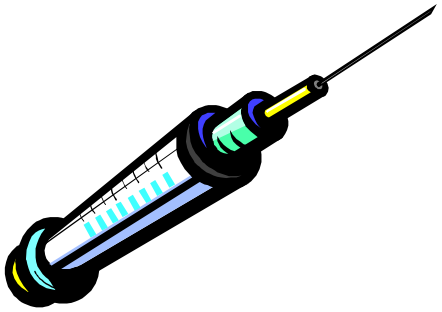
# Pediatric Labeling Benchmarks and pediatric formulations

- 2002 Best Pharmaceuticals for Children Act ( consideration for list placement if reformulation of a drug is necessary)

- 2003 Pediatric Research Equity Act (Application shall contain data using appropriate formulations for each group)

# Pediatric formulations quagmire


Adult formulations



Extemporaneous Formulations

***Adequate Formulations For age????***


Dispensing By parents

Home preparation

# NICHD Pediatric Formulations Initiative

- To identify off and on patent drugs for which no suitable formulations are available
- To determine scientific and technical barriers that prevent development of pediatric formulations
- To summarize current knowledge on drug palatability, taste masking, bitterness reduction and pediatric taste studies and identify gaps in knowledge

# Pediatric Formulations Initiative

- To determine current knowledge of the toxicity of flavoring dyes, sweeteners and preservatives
- To identify current practices for dispensing drugs without appropriate pediatric formulations and determine suitability of using different methods for oral use.
- To identify regulatory issues that affect the development and approval of pediatric formulations
- To create a forum for information exchange

# Pediatric Formulations Initiative (PFI)

- To explore possible funding mechanisms for 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
- To determine the role of NIH in facilitating the development of pediatric formulations and stimulating research in this area

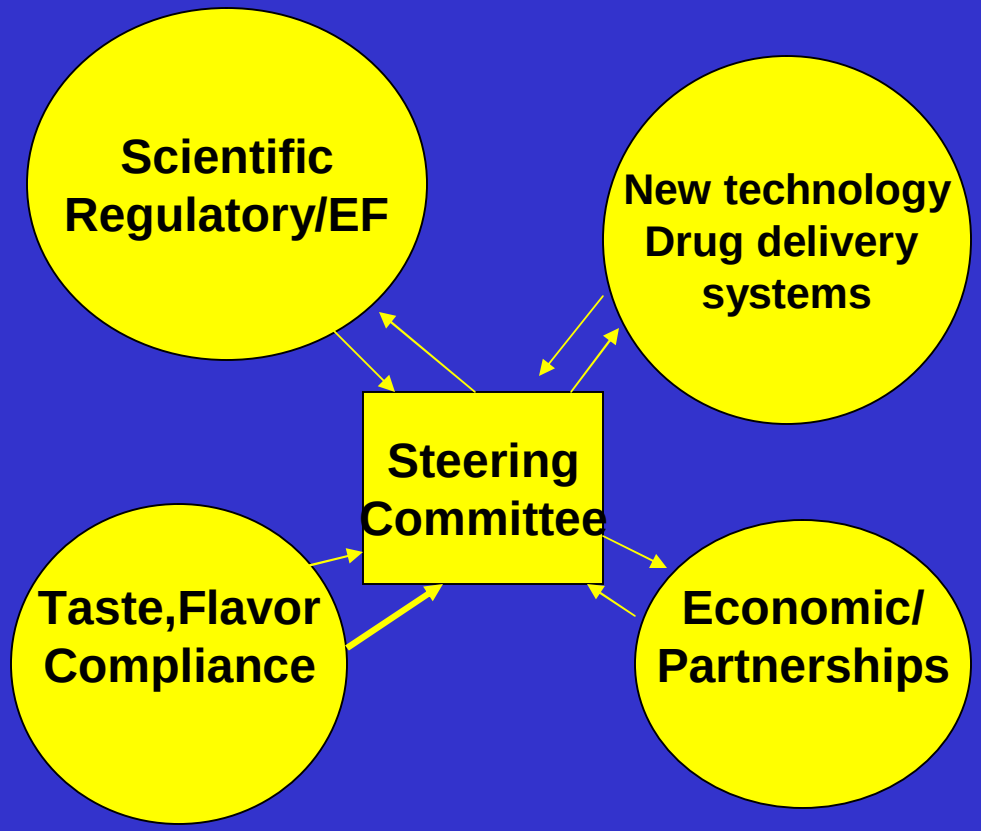
# Pediatric Formulations Proposed Initiative

- To identify and promote the development and application in pediatrics of new methods of drug delivery
- To determine the role of extemporaneous formulations and how the effectiveness and safety of these preparations can be realistically monitored.
- To identify economic barriers and possible solutions

# Pediatric Formulations Initiative

WEBSITE:www.circlesolutions.com/bpcapf

## Working Groups



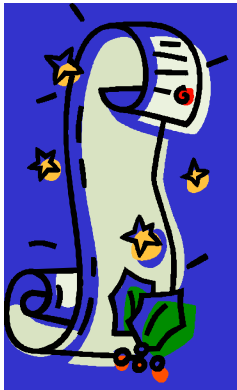
# Pediatric Formulation Initiative

## Approach

- On-going process
- Establish technical focus groups June 2005
- First Planning session held in Dec. 2005 Recommendations and actions implemented
- Creation of Task Specific Groups

# Scientific, technical and regulatory barriers work group

- Scope of the problem of lack of appropriate formulations
- Appropriate formulations for developmental age
- Problems associated with the used of extemporaneous formulations. Current practices



# Scope of the problem

- Total Number and type of formulations needed
- Number and type of formulations by developmental age group
- Need for similar type of formulations in neurologically compromised and geriatric patient population

# Compounded preparations for pediatric use: practitioner survey (2006)

- Prepared by  scientific, regulatory WG
- Administered and analyzed by USP
- Includes geriatrics (input by National Institute on Aging)
- Sent to Hospitals, independent community, chain pharmacies and nursing homes

# Are oral liquid preparations the gold standard for young infants and children?

- Can other fast dissolving oral formulations partially replace them?
- What is the role of alternative drug delivery systems?

# Novel dosing instruments

**Syringes**


**Droppers**


**Pacifier**


Nystatin suspension, Bioglan

**Dropper tube**


Codeine drops, Abbott

*J. Breitkreutz*

# Buccal drug preparations

1. Fast-dissolving drug formulations (FDDF)
2. Self-emulsifying drug delivery systems (SEDDS), Melting tablets
3. Chewable tablets
4. Softchews / multifunctional tablets
5. Mucoadhesive strips
6. Lollipops

1.


2.


3.

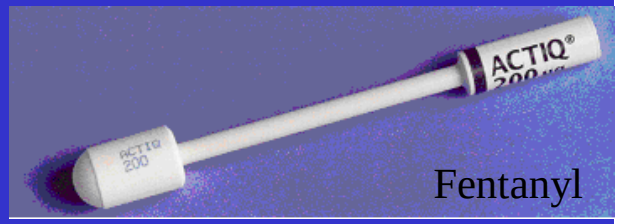

Montelukast

4.


5.


Dextromethorphan

6.




Fentanyl

# Dosage forms that could be used Pediatrics

## Alternatives to tablets and capsules

(L Buhse)

- Freezer pops
- Gummy gels
- Oral granules
- Oral effervescent granules
- Chewing gums
- Troches

# Appropriate formulations for age

Not well defined/studied

EMEA formulations group: initial draft attempt to deal with the problem


# PREFERRED DOSAGE FORMS

**Formulations of choice for the pediatric population, EMEA 2005**

| | PRETERM | TERM | INFANTS & TODDLERS | CHILD PRE-SCHOOL | CHILD SCHOOL | 12-18 |
|---|---|---|---|---|---|---|
| **DROPS** | ++ | ++++ | +++++ | +++++ | +++ | ++ |
| **LIQUID** | ++ | ++ | +++++ | +++++ | +++ | ++ |
| **MULTI-PARTICULATE** | + | ++ | ++ | ++++ | ++++ | +++++ |
| **TABLET** | - | - | + | +++ | ++++ | +++++ |
| **CHEW TABLET** | - | - | + | +++ | +++++ | +++++ |
| **'MELT' TABLET** | - | + | ++++ | ++++ | +++++ | +++++ |

# Pediatric extemporaneous formulations:

the default option

# Risk Management Issues

# Extemporaneous Formulations

## Extemporaneous formulations Task group

- Limited  compounding and stability information (40 years to develop USP monographs for pediatric drugs)
- Stability data of syrups not done for many drugs
- Improper utilization of water
- Contamination/Sterility problems
- Companies producing syrups may change formulation
- Lack of quality control mechanism

# US and Canada Children's Hospitals Survey on the use of ET liquid formulations

- Survey developed by the ET formulations Task group
- Survey to be administered and analyzed by the Pediatric Pharmacy Advocacy Group
- A pilot study will start in a few weeks
- Thirty children's hospitals in US and Canada will be invited to participate
- Includes in patient and out patient and financial information
- Will determine extent of use and extent of deviations from published formulations
- Seek list of drugs for which stability data is needed

# Technical Focus Groups

## Overall objectives

## Economic barriers and partnerships

- To identify economic barriers and possible solutions
- To explore possible funding mechanisms for the development of academic and industry partnerships to create cost-effective and appropriately formulated products for orphan drugs and off-patent drugs and ensure their distribution and availability
- To determine the role of NICHD and other NIH institutes in facilitating the development of pediatric formulations and stimulating research in this area.

# Relatively Small Pediatric Market

- 2005 U.S. Pharma sales ~$250 Billion
  - Annual sales growth rate of 5.4%

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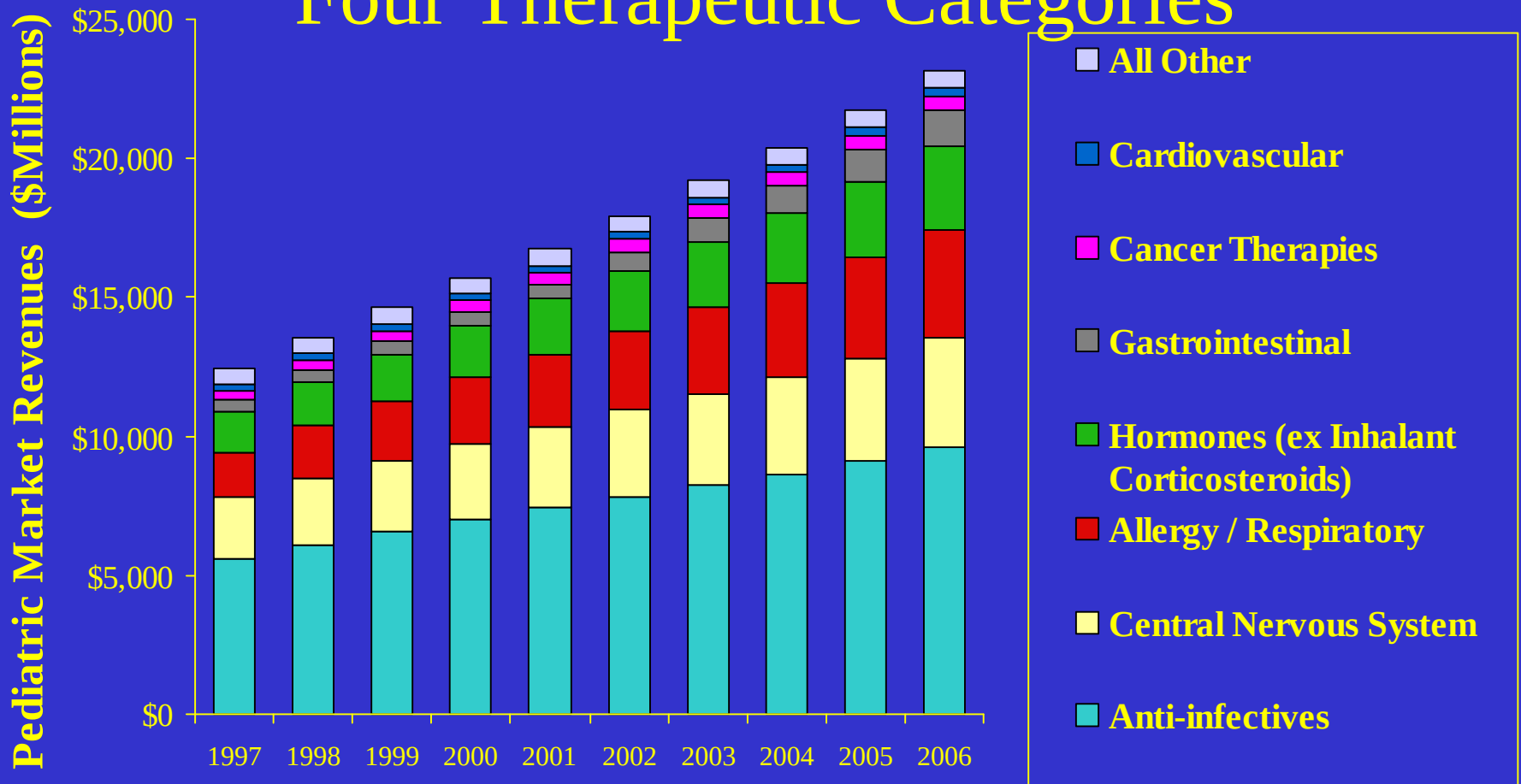
- 2005 U.S. Peds Pharma sales ~$37 Billion
  - (Kalomara)
  - Annual sales growth rate of 4%

# Pediatric Market Concentrated in Only Four Therapeutic Categories




Source: Kalorama Information The Worldwide Market For Prescription Pediatric Drugs, October, 2002

# Characteristics of Pediatric Market

- Further segmented by age groups
  - Neonates, infants, toddlers, school children, adolescents
  - Different formulations and dosing in each age group
- Majority of drugs are prescribed by pediatricians are off-label
- Significant number of drugs prescribed by pediatricians are generic (off-patent)

# Economic Barriers

- Lack of incentives
  - Small market
  - High risk and little return on investment
- Product liability
- Risks to product label
  - AEs during pediatric trials (i.e. suicide risk from SSRIs in adolescents)
- High cost of sustaining dedicated pediatric sales force
- Multiple formulations often needed to address different age groups
- Limited number of patients available for study

## Pediatric Labeling and Pediatric Formulations
## Line extension vs. pediatric specialties companies

Out of 109 Products* that recently had pediatric labeling changes :

- 95% of the companies were big pharma
  - Most of the 109 products have significant adult use
  - Small companies may not have sufficient resources for pediatric studies
  - Pediatric specialty companies do not have the incentive of adult indications
- While pediatric labeling was achieved, only 7% of the products had pediatric formulations

FDA Pediatric Drug Development. BPCA statistics page (March 26,2006)

# Pre PREA and off-patent drugs

$ 8-15 million dollars for CMC cost/ drug + cost of trials

Opinion-based estimate Economics Working group

Need for prioritization

# Economic Working group

## Possible solutions to economic barriers

- Increase the market size
  - Combine incentives for pediatric and geriatric markets
  - Development of global standards
- Reduction of cost/risk/time to market
- Use of “existing” formulations
  - Donation of NDA to not-for-profit organization
- Importation of approved pediatric drugs
  - Legal, regulatory, legislative issues need to be address
- Incentives (limited exclusivity) / funding/ tax breaks
- Incentives for priority extemporaneously formulated drugs
- Incentives for pediatric formulation of generic drugs (similar to EU drugs – 12 years data exclusivity)
- Private-public partnerships for orphan drugs

# Taste and Flavor Testing Working Group

*Objectives*: To summarize the current knowledge of sensory development, drug palatability, taste masking and bitterness reduction, the appropriateness of current pediatric taste tests, and identify gaps in knowledge.

# Taste Testing in Children

- Sensory world of children is different than adult:
  heightened preference for sweets and salt and rejection of some bitter tastes during development
- Children differ from adults in perceptual sensitivity, cognitive, emotional, and physical maturity.
- Distinguishing sensitivity from hedonic responses is difficult to do in infants and children.
- Use of electronic tongues and noses for initial screening of drugs is still in its infancy. Most of the applications of these technologies represent limited feasibility studies with poor reproducibility and predictive value.

# Gaps in Knowledge

- More research is needed to determine reliability of methods that measure sensitivity and preferences in children. What's best predictor for initial acceptance? Chronic use acceptance?
- More research is needed on texture (e.g., viscosity) perception, as it relates to medication.
- When should children be used to assess palatability and acceptance of oral medications?
- How does medication usage and disease state modify taste and smell perception?
- What is the evidence is there for a "strong association" for color and flavor? Does it impact acceptance of products?

# Gaps in Knowledge

- How does medication usage and disease state modify taste and smell perception?
- What is the evidence is there for a “strong association” for color and flavor? Does it impact acceptance of products?
- Does early and chronic exposure to drugs modify later acceptance in infants?

# Bitter Blocking and Masking New Knowledge

- A large family of taste receptor genes devoted to the detection of bitter tastes, the TAS2R genes, has been identified. Analyses of the human genome revealed that the hT2R family is composed of about 25 receptors. Each one could recognize multiple compounds, some of which are chemically related but some which are not.
- Genomic-based receptor assay systems hold significant promise for discovery of novel flavor molecules and taste blockers.
- Genomics and other new cellular and molecular techniques may lead to development of blockers for all or most of bitter transduction at one of more common elements of the pathways.

# Gaps in Knowledge

- Study of bitter and irritation perception in other parts of the oral cavity (e.g., throat). A major component of the throat irritation occurs via pH-dependent receptor mechanisms. Thus, ibuprofen and other drugs may stimulate a novel, pH-sensitive irritant system.

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# Technical Focus Group

## Areas for consideration

- Development and application of new methods of drug delivery
  - Novel alternative methods for the delivery of drugs

    Inhalation drug therapy

    Dermal delivery\Gel technology

    Dendrimers/Biopolymers

    Nanocrystal technology

    Fast melt technology

    Other methods (oral,rectal,needles drug delivery etc)

# Conclusions

-A significant number of drug formulations are not suitable for children (includes both on and off-patent drugs)

- Economic factors are the major impediment for the development of appropriate pediatric formulations

- For most drugs a suitable formulation and administration pathway may be developed

- Dosing instruments may be as important as the formulation itself

-The use of ET formulations is often unsafe

-Alternatives to oral liquid formulations are neeed

- There are major gaps in knowlege of appropriate taste drug testing in young children and of taste blocking and tasting

What is needed to solve the problem of the lack of appropriate pediatric formulations ?