PEDIATRIC FORMULATIONS: NIH-FDA COOPERATIVE EFFORTS

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FDA Pediatric Advisory Committee
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OUTLINE

- Need for Improved Oral Pediatric Formulations
- Best Pharmaceuticals for Children Act
- NICHD Efforts: NICHD-FDA Intra-Agency Agreement for an Oral Formulations Platform
<table>
<thead>
<tr>
<th>Article</th>
<th>Determination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gray's Catarrh Powder</td>
<td>Contains cocaine</td>
</tr>
<tr>
<td>Shiloh's Consumption Cure</td>
<td>Contains chloroform and alcohol</td>
</tr>
<tr>
<td>Hood's Sarsaparilla</td>
<td>Contains 17.02% alcohol by volume</td>
</tr>
<tr>
<td>Paine's Celery Compound</td>
<td>Contains 20.24% alcohol by volume</td>
</tr>
<tr>
<td>Piso's Consumption Cure</td>
<td>Contains chloroform, alcohol, and marijuana</td>
</tr>
<tr>
<td>Dr. Bull's cough syrup</td>
<td>Contains chloroform and morphine</td>
</tr>
<tr>
<td>Mrs. Winslow's Soothing Syrup</td>
<td>Contains morphine, some samples contained higher</td>
</tr>
<tr>
<td></td>
<td>concentrations of the drug</td>
</tr>
<tr>
<td>Dr. King's Consumption Cure</td>
<td>Contains morphine and chloroform</td>
</tr>
<tr>
<td>Dr. Mile's new cure for the heart</td>
<td>10.83% alcohol by volume</td>
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</tbody>
</table>
CHLOROFORM, ALCOHOL, MARIJUANA
MORPHINE
DIETHYLENE GLYCOL
HISTORY OF PEDIATRIC DRUG TRAGEDIES

- 1905: deaths from patent medicines
- 1936: sulfanilamide dissolved in diethylene glycol kills 107
- 1961: thalidomide causes limb deformities
REGULATORY ACTS

1906: Pure Food and Drug Act
  • Labels of food and drugs must truthfully identify contents (pure)

1937: Federal Food, Drug, and Cosmetic Act
  • Drugs must be safe

1962: Kefauver-Harris Amendment
  • Drugs must be effective for their labeled indication
BEST PHARMACEUTICALS FOR CHILDREN ACT: NIH

- Prioritize drugs/therapeutic areas
- Sponsor pediatric clinical trials
- Submit data to FDA for labeling changes
2002: Master List of all Off-Patent Drugs which lack adequate pediatric labeling

Consider for prioritizing:
- Availability of S/E data
- Are additional data needed?
- Will new studies produce health benefits?
- Reformulation?

Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Drugs
2007: Therapeutic Areas

Consider for prioritizing:
- Therapeutic gaps
- Potential health benefits of research
- Adequacy of necessary infrastructure

Consultation with experts in pediatric practice and research

Develop, prioritize, publish an Annual List of Therapeutic Areas and Specific Needs
PRIORITIZATION

- Many drugs and therapeutic areas
CLINICAL TRIALS

- Lorazepam for sedation
- Lorazepam for status epilepticus
- Nitroprusside for blood pressure reduction
- Baclofen (oral) for spasticity (re-formulation)
- Lithium for mania
- Meropenem for severe intra-abdominal infections in neonates (volume)
- Azithromycin for Ureaplasma infections
- Morphine for pain in neonates
CLINICAL TRIALS

- NHLBI: Hydroxyurea in young children with sickle cell disease (re-formulation)
- NCI:
  - Vincristine for pediatric malignancies
  - Actinomycin-D for pediatric malignancies
  - Methotrexate and neuro-cognition
  - Daunomycin disposition related to body mass
  - Isotretinoin for neuroblastoma (re-formulation)
INFRASTRUCTURE: PEDIATRIC TRIALS NETWORK

- Awarded September 28, 2010
- Duke University
  - https://www.fbo.gov/index?s=opportunity&mode=form&id=cf49c1b60b546914941b266295b24c84&tab=core&cview=1

- Cores:
  - Management
  - Clinical trials performance
  - Formulations development for clinical trials
  - Clinical pharmacology study design and analysis
  - Device development (validation)
FORMULATIONS PROBLEMS WITH BPCA TRIALS

- Baclofen
- Hydroxyurea
- Meropenem
- Isotretinoin
HYDROXYUREA 500 MG
ISOTRETINOIN 10 MG
EXAMPLES OF CREATIVE FORMULATIONS

- **Zyrtec**
  - **Fluorettten 0.25 mg**
  - **Triaminic Softchews**
  - **Triaminic Thin Strips**
  - **TopCare Pain Relief**

**Ingredients:**
- Dextromethorphan
- Fentanyl
PROBLEMS

- Inaccurate dosing
- Lack of stability
- Bad taste
- Adherence problems
- Lack of standardization in extemporaneous compounding
- Environmental safety from home compounding
IDEAL ORAL PEDIATRIC DOSAGE FORM

- Tasteless/taste-masked
- With minimal excipients
- In flexible dosage increments
- Orally dissolvable, or easy to swallow or dissolve in small amount of liquid
- Heat, humidity and light stable
DRUGS LACKING A PEDIATRIC FORMULATION

- Hydroxyurea
- Isoniazid
- 6-mercaptopurine, methotrexate, 6-thioguanine, isotretinoin
- L-thyroxine
- Clindamycin
- Prednisone, prednisolone
- Baclofen
- Antiretrovirals
- Meropenem (concentration, volume for neonates)
IN THE DEVELOPING WORLD

- Albendazole
- For malaria: sulfadoxine-pyrimethamine, chlorproguanil-dapsone, mefloquine
- For trypanosomiasis: benznidazole, nifurtimox
WATER, REFRIGERATION
PROBLEMS

- Technical/Scientific
- Business: potential population affected
  - Children
  - Persons with swallowing problems: elderly, stroke, cerebral palsy
PEDIATRIC FORMULATIONS 2012
NIH-FDA INTERACTIONS

- American Association of Pharmaceutical Scientists 2008
  - Formulation Design and Development
- Division of Product Quality Research Programs, FDA
NIH-FDA INTRA-AGENCY AGREEMENT: FORMULATIONS PLATFORM 2010-2012

- Provide open source, publicly available oral pediatric formulations platform
- Designate specific formulations technologies, given the molecular and chemical properties of the drug and the specific desired properties of the dosage form
TASKS

1- assess commercially available formulations
2- determine publicly available technologies
3- employ computational methods to prototypes to categorize molecular structures for various characteristics
   - Solubility, permeability
   - Stability
   - Taste (bitterness)
TASKS

4- determine optimal formulations technologies for specific drug categories
5- produce prototype batches using available technologies
6- present results in publications /presentations and on the NIH and FDA web sites
TASK 1 PUBLICLY AVAILABLE

http://b pca.nichd.nih.gov/collaborativeefforts/initiatives/index.cfm
Intra-Agency Agreement Between the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA)
Oral Formulations Platform—Report 1

The objective of this work is to provide some baseline information about marketed pediatric products that have been approved for administration to pediatric patients. These products are approved either for administration to pediatric patients as-is or by reconstitution and compounding with specific instructions on the product label. A significant amount can be learned from these approved products, and the knowledge gained can be applied for the development of new formulations of new and existing active pharmaceutical ingredients (APIs).

As part of the National Institutes of Health-FDA initiative, a list of 382 products has been compiled so far. This list was compiled based on the approved products listed on the FDA Web site (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu) or from the Sigler’s Prescription Drug Card list (SFI medical publishing, P.O. Box 3578, Lawrence, KS 66046).

A review of the currently available products indicate that the pediatric medications are available as drops, syrups, elixirs, suspensions, sprinkles, capsules, injectables, chewable tablets, orally disintegrating tablets, and powders.
## TASK 1: BCS TABLES

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<tr>
<th>#</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>BCS Class</th>
<th>References</th>
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<tr>
<td>1</td>
<td>abacavir sulfate</td>
<td>Zilagen</td>
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<td>1,2,5</td>
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<td>acetaminophen</td>
<td>Children's Tylenol</td>
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<tr>
<td>3</td>
<td>acetaminophen/codeine</td>
<td>acetaminophen/codeine</td>
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<td>1/1</td>
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<td>acyclovir</td>
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<td>Augmentin</td>
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<td>Adderall XR</td>
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<td>Agenerase (Discontinued)</td>
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</tr>
</tbody>
</table>
PROGRESS ON TASKS

1- assess commercially available formulations: completed

2- determine publicly available technologies

3- employ computational methods to prototypes to categorize molecular structures for various characteristics
   - Solubility, permeability: completed
   - Stability
   - Taste (bitterness)
TASKS

4- determine optimal formulations technologies for specific drug categories

5- produce prototype batches using available technologies: three products reformulated

6- present results in publications /presentations and on the NICHD BPCA and FDA web sites: completed tasks are on the NICHD BPCA and FDA web sites
BENEFITS OF A FORMULATIONS PLATFORM

- Children and others with swallowing problems (elderly, stroke, cerebral palsy)
- FDA: facilitate the development of novel oral dosage forms
- Industry: transparent resource to inform and facilitate production of new oral dosage forms
NICHD FUNDING OPPORTUNITY ANNOUNCEMENTS: FORMULATIONS

- Development of Appropriate Pediatric Formulations and Pediatric Drug Delivery Systems (PAR 11-301, 302, 303, 304, 305)
  - The purpose of this Funding Opportunity Announcement is to address different and complementary research needs for the development and acceptability of pediatric drug formulations in different age groups. Development and testing of novel pediatric drug delivery systems is also part of this initiative.
CONTACT INFORMATION

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