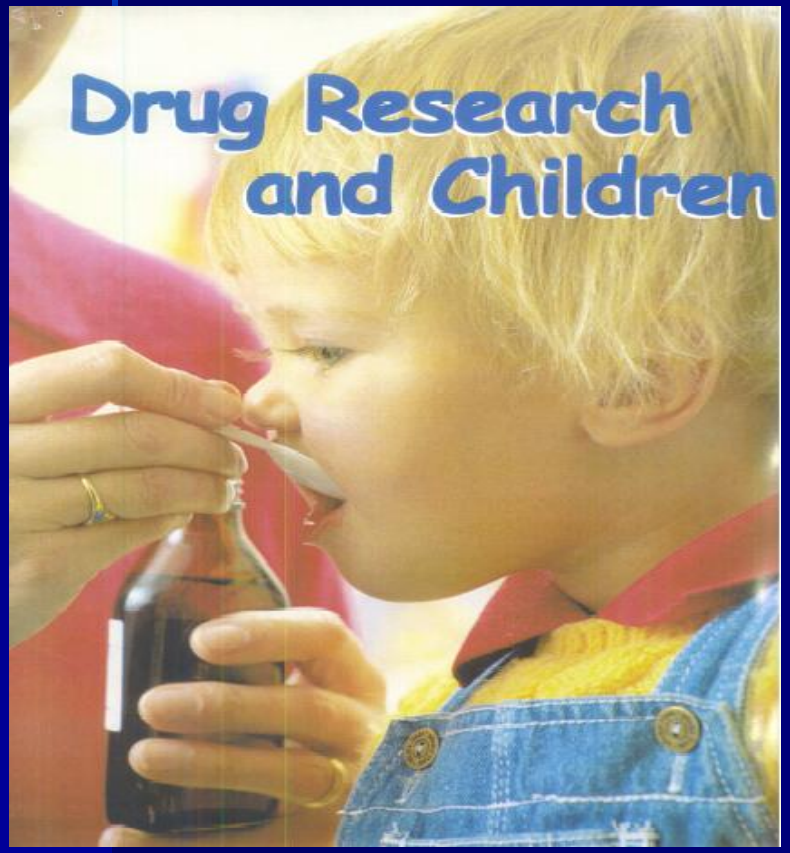
Pediatric Drug Development What have we learned?



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FDA

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The PAST: Harvey Wiley

'Father of the Food and Drugs Act' and the 'Crusading Chemist'

The Pediatric Knowledge Gap: Possible Reasons

- Ethical Concerns
- Limited populations for certain diseases
- Difficulties in conducting trials in pediatrics: logistical to technical reasons
- Belief dosing could be determined by weight based calculations (“little adults”)
- Lack of accepted endpoints and validated pediatric assessment tools
- Limited marketing potential compared to adults

Present Solutions

- Provide an incentive: pediatric exclusivity (the Written Request Process in the US) and data protection (in Europe)
- Require pediatric plans be implemented with development of products used in pediatrics
- Ensure ethical oversight
- Make the process and the data generated from the process transparent- not fully implemented
- Additional emphasis on safety assessments

Scientific Trial Issues

- Scientific Issues
  - Extrapolation
  - Bridging Studies
  - Safety Studies: length and type
  - Endpoint & Validation Issues
  - Ethical constraints of placebo controlled trials (rapid-rescue?)
  - Need for longer term outcomes for studies (18-24 months)
- Learning from the trials conducted

Why Pediatric Drug Development is Global

- SMALLER PART OF THE POPULATION: Children by definition occupy a lifespan for a shorter period of time than an adult. There are fewer of them.

- "PROTECTED FROM STUDIES": Children cannot volunteer themselves the way adults can and children without a disease or condition are not usually involved in trials.

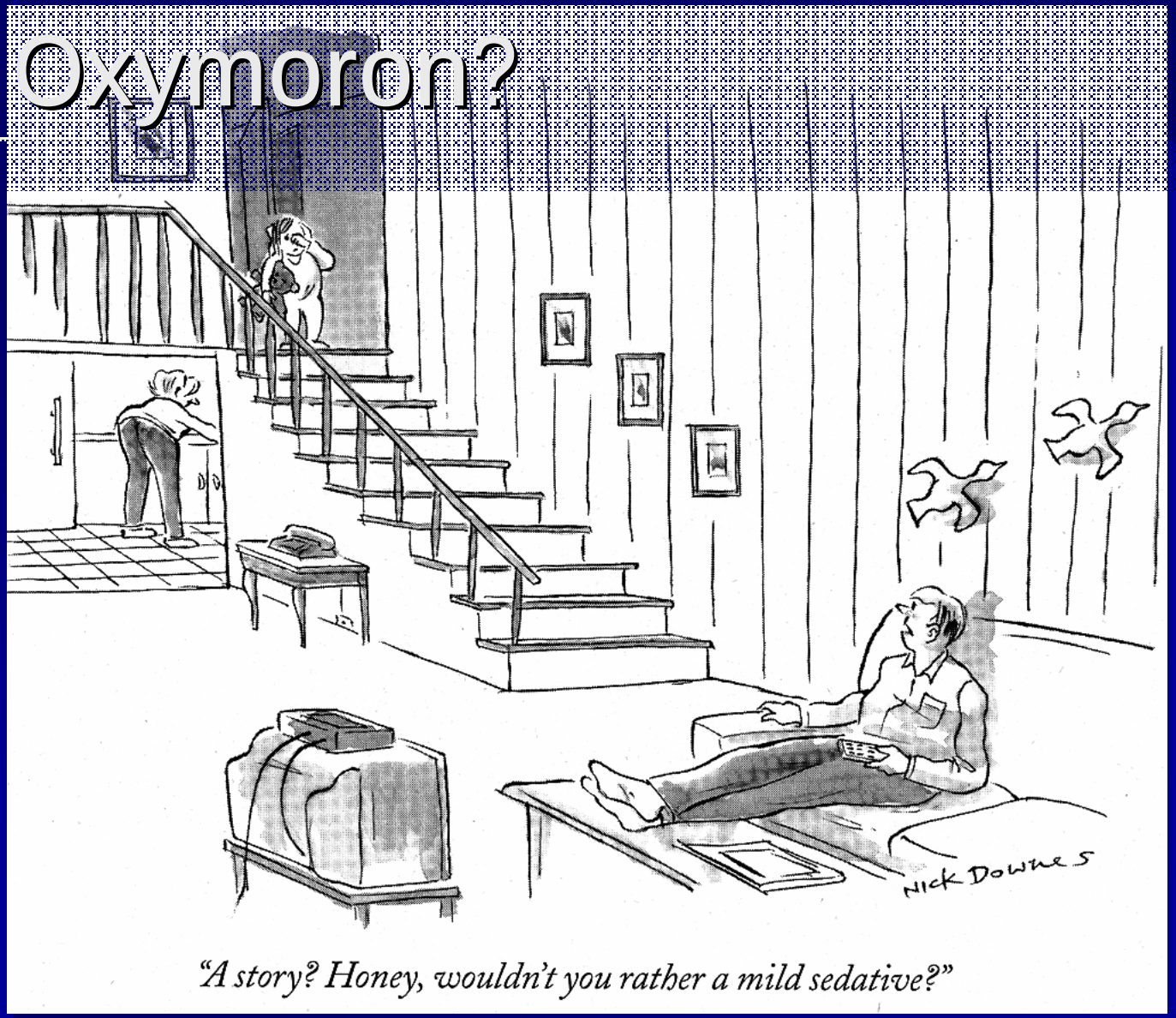
- LITTLE COMMERCIAL MOTIVATION: for companies to answer questions by performing additional pediatric studies. Thus, there are fewer pediatric studies in a product's development lifespan.

= fewer patients and a need for more experienced sites

Improvements: The Europeans have watched and learned

- Combine the incentive and requirement into one process
- Have a pediatric expert group that works on the development of all of the required pediatric studies
- Ensure focused pediatric safety reviews for all of the pediatric studies

Best Pharmaceuticals for Children – an Oxymoron?



"A story? Honey, wouldn't you rather a mild sedative?"

What Pediatric Trials Have Taught (what we were doing before we knew better)

1. Unnecessary Exposure to Ineffective Drugs
2. Ineffective Dosing of an Effective Drug
3. Overdosing of an Effective Drug
4. Undefined Unique Pediatric AE's
5. Effects on Growth and Behavior

ONGOING LESSONS LEARNED

1. PK is more variable, even within the pediatric population, than anticipated
2. Adverse reactions that are pediatric specific will not be defined without pediatric studies
3. Trial designs are being modified as we learn from submitted studies
4. Ethical issues have to be reassessed from the pediatric perspective
5. Safety studies, of sufficient duration and longer term follow-up studies, remain problematic

Important Components: for any future programs

- Labeling needs to inform the reader about the pediatric trials irrespective of approval status and irrespective of process
- Public dissemination of the studies is important, irrespective of approval status
- Timing of the Exclusivity determination should be at time of action on application
- Having focused pediatric safety reviews ensure pediatric issues are addressed
- Having a strong ethics program is critical

For the Future: Ethics

- Better definitions, using realistic examples
  - -risk categories
  - -direct benefit
  - -disorder/condition
- Refinement of assent process
- Pediatric Trial Oversight
  - -Data collection-quantify risk in the pediatric population
  - -Compliance data-quantify adherence

For the Future: Needs

- More transparency for all pediatric studies and the data from those studies
- Continued development of pediatric endpoints and assessment tools
- Real time inspections of pediatric trials
- Continued development of how to best utilize juvenile animal models
- Better approaches to assess long term safety
- Active surveillance systems focusing on pediatrics
- Studies in Neonates and prematures

The Future: Special Population Still remains largely unstudied

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