# U.S. Experience With Regard to Pediatric Legislation

Dr. Dianne Murphy

Director, Office of Pediatric Therapeutics, OC

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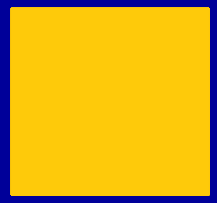

# Overview

- The problem
- Historical Efforts
- Legislative Fixes
- Results from Studies in Children
- Continuing Challenges

# The Problem

There is inadequate information regarding Pediatric use for almost ¾ of prescription medications

Gilman:  Clinical Pharmacokinetics 1992

# The Problem
# N=1

- Ignorance is poor public policy and yet it best describes what has been the status of therapeutics in the pediatric population
- Each child became an experiment of 1 and there was little knowledge gained for the entire population using a therapy

# The Knowledge Gap in Pediatric Therapeutics

- How did we get to this state of ignorance?
- Why was it acceptable that a population that is growing, developing and inherently highly variable would not be studied while the more stable, not growing and less variable adult population was?

# The 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

# Why is it a Problem?

## Neonates

- Average Number of Drugs Given
  - <1000 grams – 15-20
  - >2500 grams – 4-10
  - Over 90% of drugs used in the NICU are off-label
  - Number of Pediatric Studies (As of October 2004)
  - WR for 295 products
  - 113 products for which studies have been submitted
  - Number of Neonatal Studies
  - Only 18 of 113 drugs with data submitted for exclusivity were studied in neonates

# Why is it difficult to study Neonates?

- Technical Challenges
- Problems with surrogate markers that change with age and/or time
- Unique diseases at the time of birth
- Confounding issues related to multiple diagnoses and multiple medications
- Perception of established standard of care
- Ethical constraints

# AAP – 1977 Committee on Drugs

- It is unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children
- It is not only ethical, but also imperative that new drugs to be used in children be studied in children under controlled circumstances so the benefits of therapeutic advances will become available to all who need them

# Pediatric Benchmarks

- 1977 AAP, Committee on Drugs
- 1979 Pediatric Use Sub-Section
- 1992 Proposed:  Pediatric Labeling and Extrapolation
- 1994 Final:  Pediatric Labeling and Extrapolation
- 1997 Proposed Rule:  Pediatric Studies Required
- 1997 Food and Drug Administration Modernization Act (FDAMA) Exclusivity Incentive
- 1998 Final Rule:  Pediatric Studies Required

# History of Pediatric Regulations/Legislation

- January 2002
  - FDAMA Exclusivity Sunsets
- January 2002
  - Best Pharmaceuticals for Children Act (BPCA)
- October 2002
  - Pediatric Rule enjoined
- December 2003
  - Pediatric Research Equity Act (PREA)

# Results

# Results
# October 2004

- Products issued Written Requests: 295
  - Number of studies requested: 687

- Products with submitted studies: 113
- New Labels with Pediatric Information: 84

- Number of Children Involved: 42,939
  - Not including 40,000 in safety study of Ibuprofen

# Growth and Development
## Examples

- Prozac (Fluoxetine): in a 19-week trial effects on ht & wt were statistically significant and new directions for monitoring placed in label
- Strattera (Atomoxetine): weight percentile decreased over 18 months of treatment and appeared to be correlated with poor metabolizers

# New Adverse Events
## Examples

- Accutane – bone demineralization
- Rebetron – increase in suicidal ideation & attempts
- Elidel – increase in infections, fever & diarrhea
- Ultane – rare cases of seizures without previous history
- Gabapentin – emotional lability, hostility and thought disorder
- Propofol – increased mortality in Peds ICU & serious bradycardia when used with Fentanyl
- Betamethasone – adrenal-axis suppression
- Antidepressants - suicidality signal

# New Dosing Recommendations

## Examples

- Neurontin (Gabapentin): higher doses in children < 5 years
- Lodine (Etodolac): higher than expected doses required in younger children (2x the lower dose in adults
- Luvox (Fluvoxamine): adolescents need higher doses than previously recommended and girls 8-11 may have been overdosed

# What We Have Learned About What We Were Doing

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

# Unnecessary Exposure to Ineffective Therapies

a) Many therapies for treatment of depression
b) Navelbine (Vinorelbine) for recurrent, solid, malignant tumors
c) Detrol LA (Tolterodine) in pediatric patients 5-10 years of age
d) Buspar (Buspirone) for general anxiety disorder
e) Camptosar (Irinotecan) in previously untreated rhabomyosarcoma

# Ineffective Dosing of an Effective Therapy

a) Higher dosing required for adolescents taking Luvox (Fluvoxamine) and children <5 years taking Neurontin (Gabapentin)

b) Higher clearance of Lotensin (Benazepril) in hypertensive children

c) Double the clearance rate of Ultiva (Remifentanil) in neonates

# Overdosing of an Effective Therapy

a) Dosing of Luvox (Fluvoxamine) in girls 8-11 years of age
b) Reduced clearance of Arava (Leflunomide) in pediatric patients <40 kg
c) Decreased clearance of Pepcid (Famotidine) in infants 0-3 months of age and of Epivir (Lamivudine) for HIV in 1 week old neonates

# Undefined Unique Pediatric Adverse Effects

a) Occurrence of rare seizures in patients without a prior history of seizures when exposed to Ultane (Sevoflurane)

b) Hypopituitary Adrenal axis suppression with Diprolene (Betamethasone)

c) Increase of suicidal ideation with Rebetron (Ribavirin/Intron A)

# Effects on Growth and Developmental Behavior

a) Detrol LA (Tolterodine); Hyperactive behavior and attention disorder occurred 3 times as frequently in treated vs. placebo population
b) Decreased growth rated described for Prozac (Fluoxetine), Effexor (Venlafaxine) and Rebetron (Ribavirin/Intron A)
c) Decreased bone density in patients 12-17 year olds, treated with Accutane (Isotretinoin)

# What Have We Learned

- Drugs have historically been used in children WITHOUT the same level of evidence as has been obtained for adults and this is not good public policy
- Children are even more dynamic and variable than anticipated
- New legislation is having a positive impact on development of therapies for children
- These pediatric initiatives have identified some gaps and how much we don’t know

# ONGOING LESSONS LEARNED

1. Pharmacokinetics are more variable than anticipated
2. Adverse reactions that are pediatric specific are being defined
3. Trial designs are being modified as we learn from submitted studies
4. Ethical issues have to be reassessed from the pediatric perspective

# Ethical Issues

- Pediatric Advisory Subcommittee Meetings have addressed:
  - Patients vs. subjects in pediatric trials (11/15/99)
  - Placebo controlled trials (9/11/00)
  - Vulnerable pediatric populations (4/24/01)
- Consensus statements: http://www.fda.gov/cder/pediatric/index.htm#advisory
- Subpart D Referrals from IRB's

# General Principles

## ICH E-11

- Pediatric patients should be given medicines that have been properly evaluated for their use in the intended population
- Product development programs should include pediatric studies when pediatric use is anticipated
- Pediatric development should not delay adult studies nor adult availability
- Shared responsibility among companies, regulatory authorities, health professionals, and society as a whole

# FDA Web Page


Food and Drug Administration Home Page - Microsoft Internet Explorer provided by OITSOFT for F
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Medical Devices
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Biologics
Vaccines, Blood Products...
Animal Feed and Drugs
Livestock, Pets...
Cosmetics
Safety, Labeling...
FDA NEWS
Investigation Implicates More Counterfeit Lipitor
Program to Streamline Cancer Drug Development Announced
OTC Drugs Committee to Discuss Ipecac
Safety Alerts and Recalls
Product Approvals
More FDA News
Press Releases, Meetings, Speeches, More
Let Us Hear From You
Report a Problem with a Product
Comment on Proposed Regulations
Petition FDA
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Code of Federal Regulations
Federal Register
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Clinical Trials
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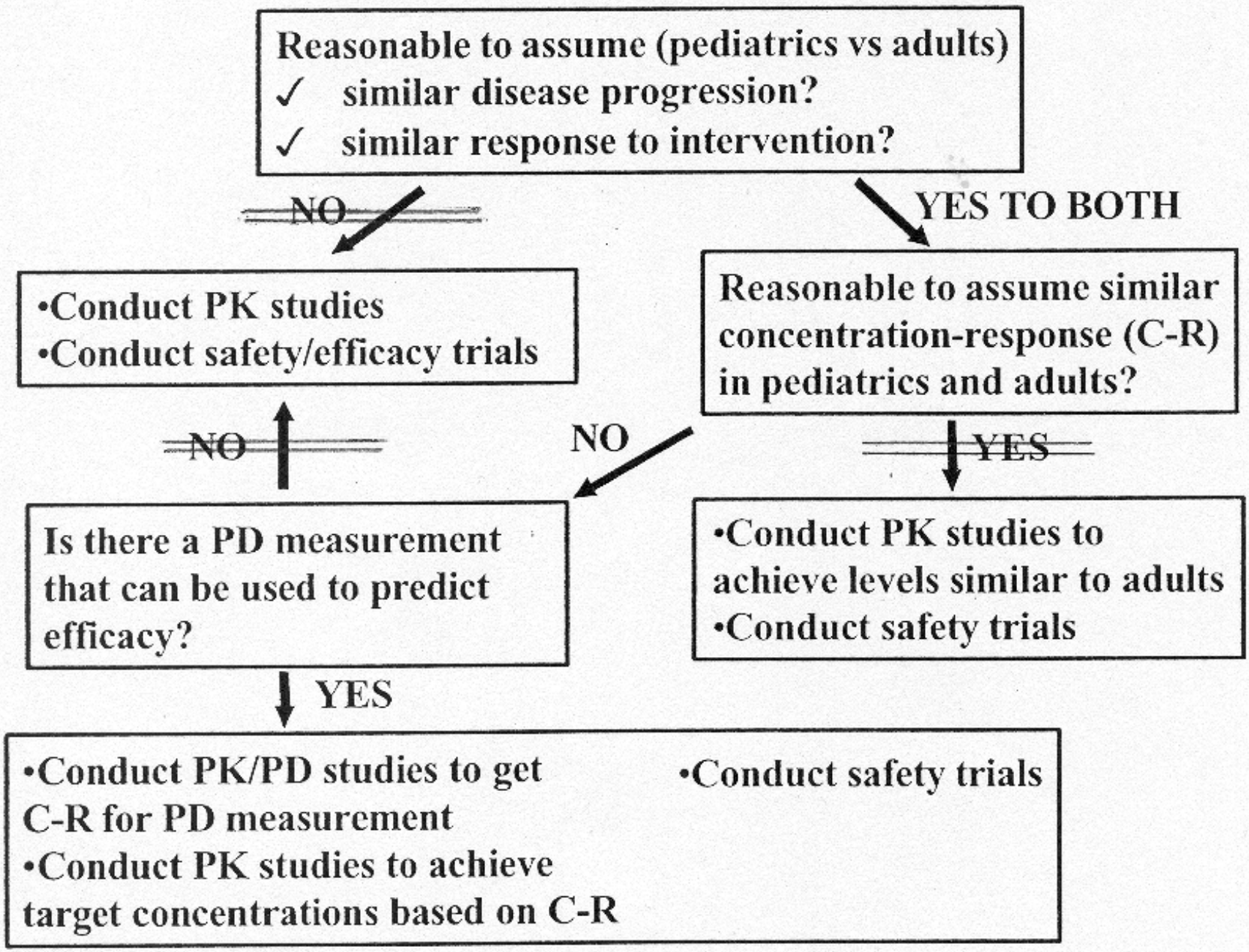
# Example 1: Pediatrics Bridging

- Anti-arrhythmic with class II (beta-blocker) and class III properties
- Approved indication in adults:  Life threatening ventricular arrhythmias
- Sponsor sought same indication in pediatrics
- Biomarker for Efficacy:  QTc change

# *Pediatric Study Decision Tree*



# Studies in Pediatrics with SVT/VT

**PK Study**

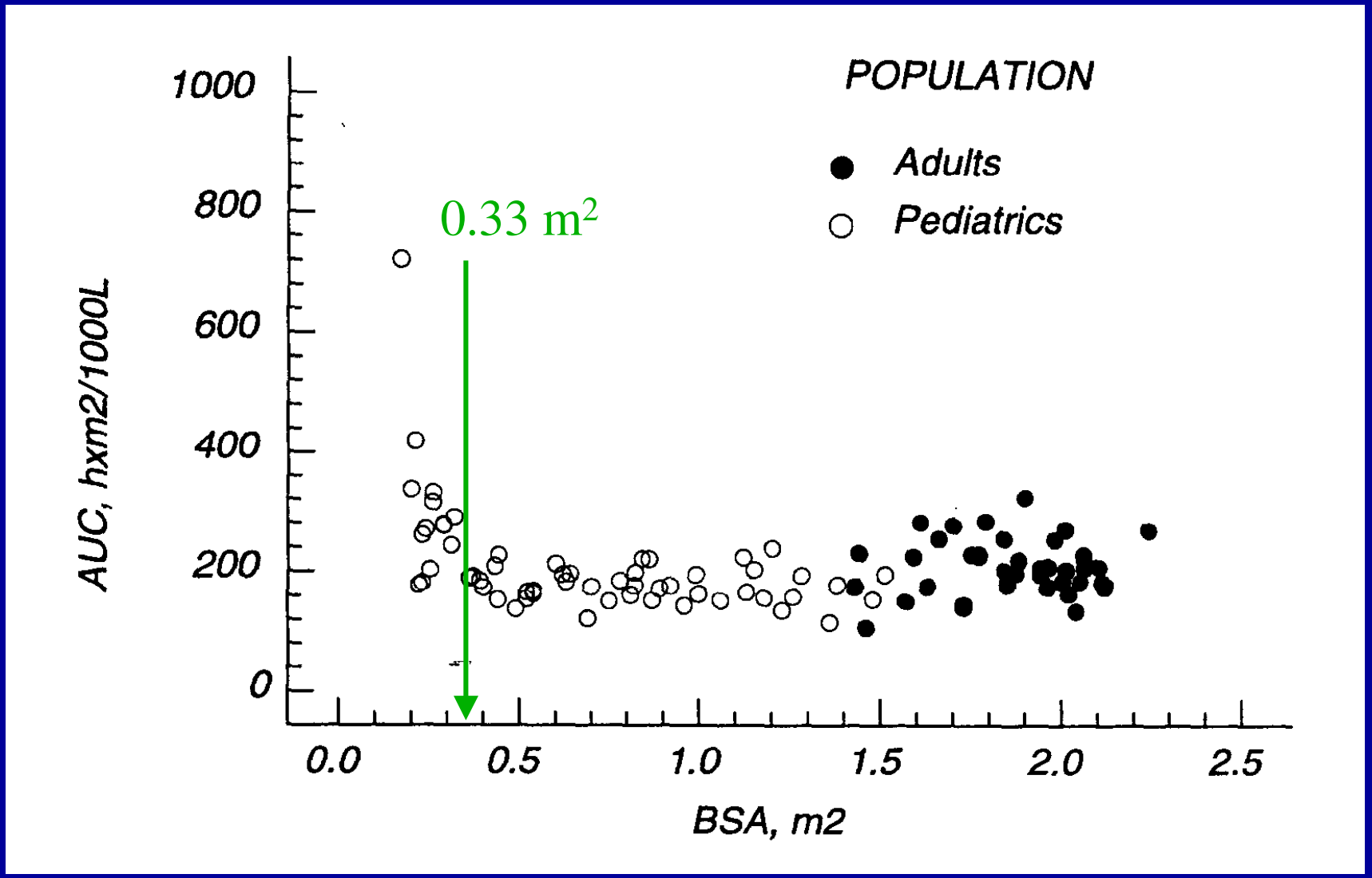
- Multi-center
- 70 mg/m$^2$ single-dose
- Only PK
- 10 plasma samples

**PK/PD Study**

- Multi-center
- Escalating doses
- 10, 30, 70 mg/m$^2$ q8h
- PK / QTc, RR
- 4 plasma samples

Age groups: neonates, infants, pre-school, school-age

# PK in Pediatrics




***Per BSA dosing for peds with BSA>0.33 $m^2$ offers comparable exposure as in adults***