

Modeling & Simulation for Pediatric Investigation Plans (PIPs):

challenges and opportunities for drug development



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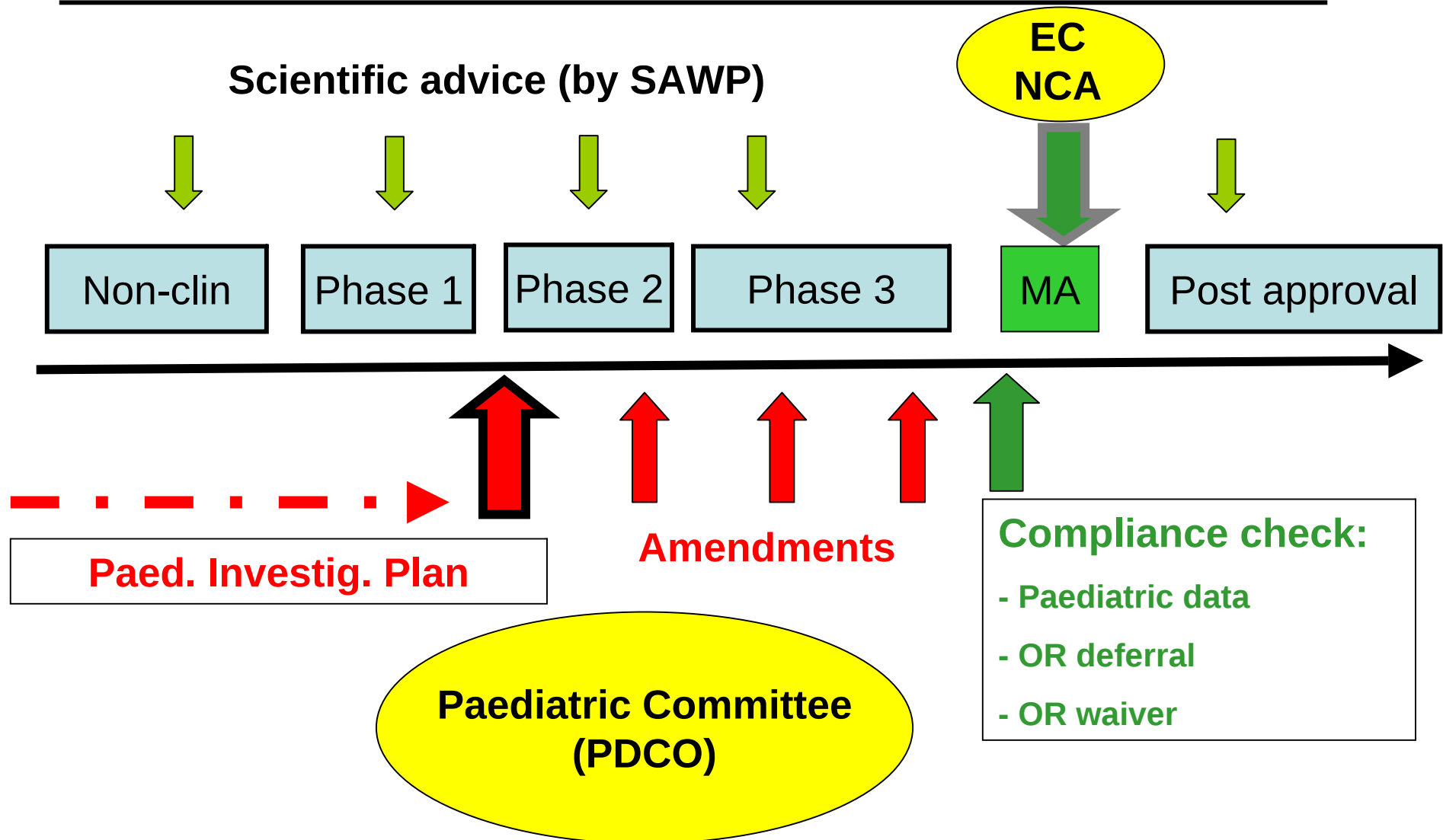


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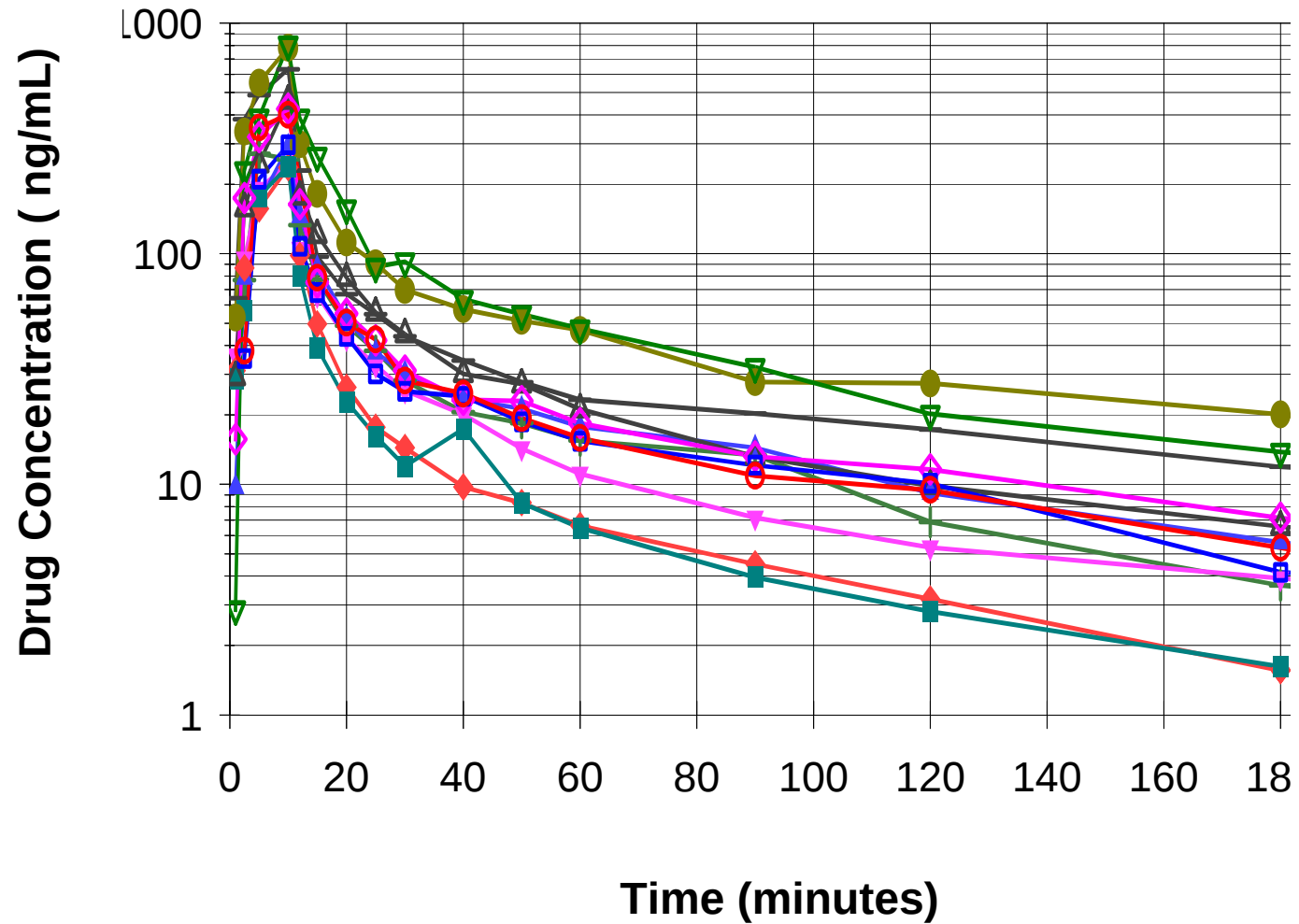
Conflicts & Disclaimers

- On sabbatical from U of Utah at Novartis
 - Funding from Utah and Novartis
 - Funding from other pharma companies in the past
- Opinions expressed are mine
 - Utah as member of NIH Pediatric Pharmacology Research Units
 - Novartis experience reviewing PIPs and responses from EMEA & PDCO

EMA PIP Time line



Typical Phase I PK Experiment in Adults



What is known at EOP1(maybe)...

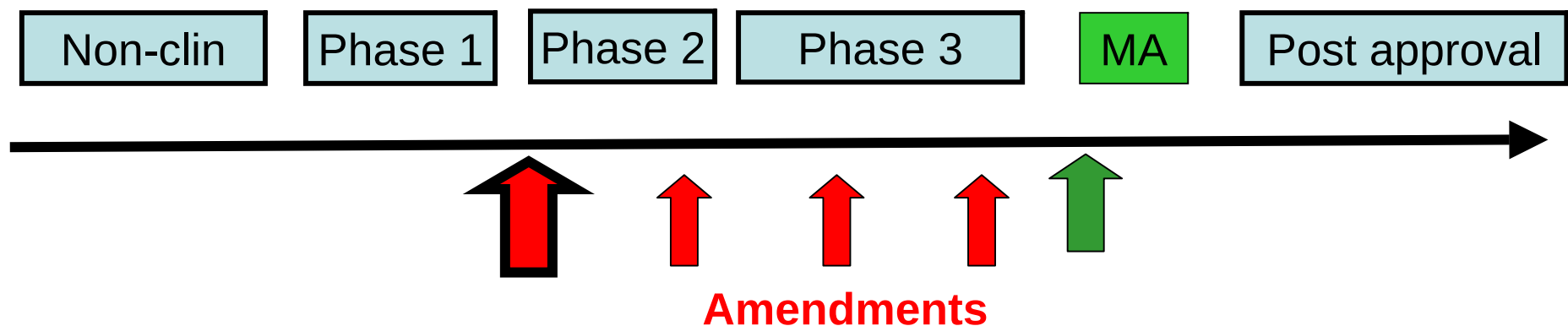
- Preclinical pharmacology
- Dose-exposure in healthy adults
- Impact on a biomarker of interest (?)
- Some idea of drug effect (?)
- Perhaps some indication of metabolism (?)

What needs to be known...

- Dose-exposure in adult *patients*
- Dose-exposure-response similarity (or not) between adult and pediatric populations
- Differences in exposure across pediatric age groups
- Scalability of biomarker of interest or concentration – effect relationship

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“Established” M & S for PIPs

- Allometric scaling from Adult PK when rational
 - Many examples presented
- Incorporation of known/expected maturation affects on disposition
 - Example of Famvir
- Bridging between known and unknown data
 - Example with Trileptal
- Impact of limited resolution
 - PK Assay LLOQ
 - Dose selection and discretization

“Emerging” M & S for PIPs

- PBPK as means to bridge preclinical and early dosing information
- Mechanism-based modeling to enhance understanding of exposure-effect relationship
- In silico approaches to anticipate differences in pediatric patients
- Novel statistical methods for maximizing information from limited populations

PIP Amendments are a dialogue

- Dialogues can be difficult
- PIP adaptation may be needed as more knowledge is gained in adult trials
- Sponsors must provide support and rationale to help HAs understand adaptations based on pharmacometrics
- HAs need to integrate this understanding into decision making and action

Are HA's ready for the dialogue?

GUIDELINE ON THE ROLE OF PHARMACOKINETICS IN THE DEVELOPMENT OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION

EXECUTIVE SUMMARY

This guideline provides advice on the use of pharmacokinetic studies in paediatric drug development and on methodological issues concerning pharmacokinetic studies in paediatric patients.

1. INTRODUCTION (background)

An application for paediatric use of a medicinal product should include sufficient information to establish efficacy and safety. Paediatric patients have the same right to well investigated therapies as adults. There are, however, several reasons why it is more difficult to study a medicinal product in paediatric patients, particularly in very young patients. Hence, it is often unrealistic to expect the applicant to fully demonstrate efficacy and safety in paediatric patients in clinical studies. In such a situation pharmacokinetic data may be used to extrapolate efficacy and/or safety from data obtained in adults or in paediatric age groups other than the age groups applied for.

Special consideration is often necessary when performing pharmacokinetic studies in paediatric patients and it is important that the pharmacokinetic information available is presented and used in an optimal manner. A specific feature of very young paediatric patients is rapid maturation of organ functions important for drug absorption, distribution, and elimination. Therefore changes in dose may be necessary for a patient over time, based on individual maturation.

It should be recognised that documenting a drug for paediatric use involves a multitude of choices and that, at present, knowledge and experience in this field is limited. Sponsors are encouraged to explore new approaches in the development of drugs for the paediatric population.

Is Industry ready for the dialogue?

Communicating With the FDA: The “Third Rail” of a New Model for Drug Development

Donald R. Stanski, MD, and John J. Orloff, MD

Keywords: *Drug development; biomarkers; modeling and simulation; FDA; communication*

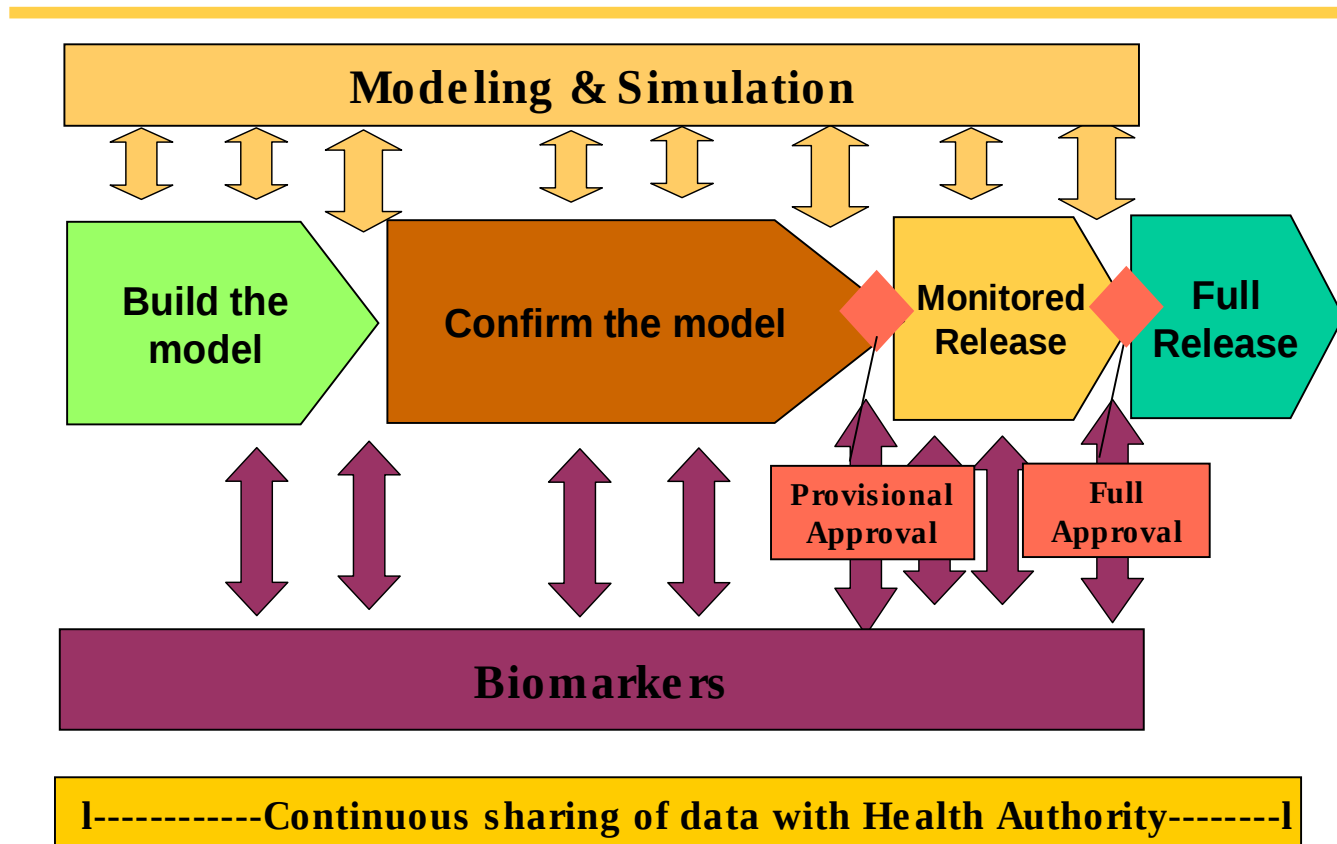
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In this issue, Wang and colleagues present a new program, the End-of-Phase 2A (EOP2A) meeting, that has been piloted at the Food and Drug Administration (FDA) during the past several years.

FDA has been limited, the feedback presented by Wang and colleagues suggests a highly valuable experience that in many cases altered the design of the clinical drug development program.

Novartis Model-based Drug Development

The Novartis Long Term Vision of Model Based Drug Development



Third Rails



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Third rail (metaphor)

From Wikipedia, the free encyclopedia

The phrase **third rail** is a [metaphor](#) in [politics](#) to denote an idea or topic that is so "charged" and "untouchable" that any [politician](#) or public official who dares to broach the subject would invariably suffer politically.

The [third rail](#) in a train system is the exposed electrical conductor that carries high voltage power. Stepping on the high-voltage third rail usually results in [electrocution](#). The use of the term in politics serves to emphasize the "shock" that results from raising the controversial idea, and the "political death" (or [political suicide](#)) that the unaware or provocative politician would encounter as a result.



This third rail, used to power trains, carries hundreds of volts of electricity, resulting in a spectacular electrocution and likely death for anyone who touches it. Third rail political issues are similarly "charged".

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Third rail for the future - power or shock?

- Use modeling & simulation to bridge between what we know and what we don't
- Establish “best practices” in approaches
- Develop studies that require the fewest possible numbers of subjects
 - “Waste not a drop...”
 - Tradeoff of utility vs. futility
- Maximize our use of quantitative knowledge

Waste not a drop...

Table 2. Trial Design Characteristics and Subject Response to Therapy

Characteristic	Amlodipine	Enalapril	Fosinopril	Irbesartan	Lisinopril	Losartan
Primary end point	Systolic	Diastolic	Systolic	Systolic	Diastolic	Diastolic
Dosing range	2	32	6	9	32	20
Success	Negative	Positive	Negative	Negative	Positive	Positive
Sample size	268	110	253	318	115	177
Low-dose change, SBP	7.48	7.04	11.15	13.58	3.47	3.42
Low-dose change, DBP	3.72	6.35	4.25	5.92	5.64	5.01
Medium-dose change, SBP	8.77	6.61	11.06	11.01	7.94	7.82
Medium-dose change, DBP	4.41	8.91	3.77	3.67	7.1	8.45
High-dose change, SBP	...	12.52	11.95	9.2	10.82	6.25
High-dose change, DBP	...	14.87	5.88	3.2	11.97	8.64
Dosing						
Low	2.5 mg	0.625 mg if <50 kg; 1.25 mg if ≥50 kg	0.1 mg/kg up to 40 mg	0.5 mg/kg	0.625 mg if <50 kg; 1.25 mg if ≥50 kg	2.5 mg if <50 kg; 5.0 mg if ≥50 kg
Medium	5 mg	2.5 mg if <50 kg; 5 mg if ≥50 kg	0.3 mg/kg up to 40 mg	1.5 mg/kg	2.5 mg if <50 kg; 5 mg if ≥50 kg	25 mg if <50 kg; 50 mg if ≥50 kg
High		≤20 mg if <50 kg; ≤40 mg if ≥50 kg	0.6 mg/kg up to 40 mg	4.5 mg/kg	20 mg if <50 kg; 40 mg if ≥50 kg	50 mg if <50 kg; 100 mg if ≥50 kg

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

Back to the future

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COMMENTARY

Hypothesis: A single clinical trial plus causal evidence of effectiveness is sufficient for drug approval

Carl C. Peck, MD, Donald B. Rubin, PhD, and Lewis B. Sheiner, MD *Washington, DC, Cambridge, Mass, and San Francisco, Calif*

In 1997, President Clinton signed the Food and Drug Administration Modernization Act of 1997 (FDAMA). Among its many provisions, section 115a amended the Federal Food, Drug, and Cosmetics Act to permit determination of substantial evidence of effectiveness as required for approval of a new drug to be based on "data from one adequate and well-controlled investigation and confirmatory evidence."* This language con-

trasts to the statute's previous wording, introduced in the 1962 amendment, that required "adequate and well controlled investigations"² (note plural, emphasis added) and interpreted by the US Food and Drug Administration to require (at least) 2 such trials. Exactly how the new mandate of FDAMA 1997 should be interpreted has since been a matter of as yet unresolved debate (see, for example, Peck and Wechsler³). The

The Pediatric Challenge

- Factors in pediatric drug development challenge “traditional” methods of drug evaluation trials
 - “Volunteer” studies are with patients
 - Limited sampling volumes
 - Challenges in consent
 - Challenges to placebo trials
- Doing more with less
- Risks of futility

The Pediatric Opportunity

- Greater acceptance by Health Authorities of pharmacometric methods for pediatric drug development
- Better methods of drug development for all populations
- Greater acceptance by Health Authorities of pharmacometric methods for **ALL** drug development

Conclusion

- Use of M & S in pediatrics is increasing
- Role in design & analysis of drug studies in pediatrics
- Methodologies to be continually evaluated, refined, tailored
- Joint responsibility and effort of industry, health authorities, and academia