Brief Selective History of Pediatric Initiatives in the United States of America

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- 1972- Former Food and Drug Administration Commissioner Charles Edwards states at the annual meeting of the American Academy of Pediatrics that most prescription products used in children are given empirically
- 1973- The National Academy of Sciences issues a report calling for innovative investigative programs to provide information on the use of pharmacologic agents in the pediatric population
- 1974-American Academy of Pediatrics issues a report commissioned by the Food and Drug Administration on the evaluation of drugs to be used for the treatment of pregnant women, infants and children
- 1975- Professor John Wilson publishes a survey of prescription drug package inserts that notes that 78 per cent of package inserts state that the product had either not been studied in infants and children or had no pediatric statement
- 1977-Publication of three documents related to pediatric research
    - Food and Drug Administration publishes guidance document on "General Considerations for the Clinical Evaluation of Drugs in Infants and Children"
    - National Commission on Pediatric Research issues "General Considerations for the Clinical Evaluation of Drugs in Infants and Children"
    - American Academy of Pediatrics issues "Guidelines for the Ethical Study of Drugs in Infants and Children"
- 1979-Food and Drug Administration publishes a regulation adding a pediatric use subsection in the precautions section of the approved product package insert
- 1983-Orphan Drug Act establishes the precedent of the Federal government providing incentives to develop new therapeutics for underserved populations
- 1994-Food and Drug Administration revises pediatric use regulation to allow extrapolation of adult efficacy data if the disease course in adults and children are similar
- 1994-National Institute of Child Health and Human Development establishes the first national network for pediatric pharmacology
- 1995- American Academy of Pediatrics revises "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations"
- 1996-Food and Drug Administration issues guidance document on the "Content and Format of Pediatric Use Section"
- 1996-National Institutes of Health(NIH) initiates a policy of requiring NIH funded clinical research to address applicability to pediatric populations
- 1997- Food and Drug Administration Modernization Act establishes incentive program for pediatric studies for medicinal products using a mechanism whereby the

Food and Drug Administration issues a pediatric Written Request for relevant studies to the product sponsor and the recipient of the Written Request submits a formal response as a study report to the Food and Drug Administration for a determination as to whether the study report fairly responds to the Written Request and qualifies for the incentive. The program is limited to chemical moities and excludes biologicals and some antibiotics.

- 1998- Food and Drug Administration publishes a regulation ("The Pediatric Rule") mandating pediatric studies when the disease or condition is similar in adults and children and if either widespread use is anticipated or the product is a therapeutic advance
- 2002-Federal Court in the District of Columbia invalidates the 1998 Pediatric Rule
- 2002-Best Pharmaceuticals for Children Act renews the pediatric incentive program and establishes a program for the study of off patent products through the National Institute of Child Health and Human Development at the National Institutes of Health
- 2003-Pediatric Research Equity Act establishes the principles of the 1998 Pediatric Rule as law that includes drugs and biologicals but excludes products with Orphan Drug designation
- 2006-Food and Drug Administration under the incentive programs had revised product package inserts for 118 products with new pediatric information
- 2007-Food and Drug Administration, as of March 19, 2007, had granted an incentive for pediatric studies to 136 products for 129 active chemical moities of 149 determinations (91% favorable determination rate)
- 2007- Food and Drug Administration, as of March 30, 2007, had revised product package inserts for 55 products under the Pediatric Research Equity Act
- 2007-Food and Drug Administration, as of March 31, 2007, had issued 340 Written Requests for pediatric studies since the incentive program began

As of March 1, 2007 73 products that received a pediatric incentive had Food and Drug Administration (FDA) reviews publicly available on the FDA Internet site. Those products that had received an incentive and had a medical review or pharmacology review or both publicly available were analyzed in further detail to determine the type and scope of studies required to qualify for the incentive, to determine the scope of disease categories and patient populations, and to ascertain any relationship between the resources required for qualifying for an incentive and the resources for a change in the approved product package insert (label).

Data from 195 individual studies across 33 drug classes in 12 disease categories was examined in detail. Of the 73 products, 57 had changes in the product label and 16 did not. There was no difference in the number or type of studies, number of patients studied, or disease categories for the products that had labeling changes compared to those that did not. The average number of studies per product was 2.6 $\pm$ 1.7 (range 1-9) and the average number of total patients enrolled per product was 357 $\pm$ 341 (range 11-1547). The total number of patients enrolled for all products was about 25 000.

Studies were classified as pharmacokinetic (PK) if only pharmacokinetics were determined, PK and pharmacodynamic (PD) if pharmacokinetic measurements and PD assessments were made, PD if only pharmcodynamic assessments, including clinical outcomes, were made,

and efficacy if a study was designed and implemented with a clinically relevant outcome measure and adequately powered to formally establish efficacy. The distribution of study types was:

Study Type	PK	PK-PD	PD	Efficacy
Total	37	34	54	64

Of the total, 54 studies were described as randomized with 33 of them to establish efficacy.

The age distribution of study enrollment had a peak at the 11-16 year old age group. The totals are:

Age Group	0-6 m	7 m-2 y	3 – 5 y	6-10 y	11-16 y	> 16 y
Total	35	37	44	50	60	42

The same age distribution was seen across all study types (PK, PK-PD, PD, and Efficacy).

For the 12 disease categories, the number of products, number of studies and number of patients are compared in the following table.

Disease Class	Products	Studies	Average (Mean) studies per product	Total Enrolled	Average (Mean) pts per product	Average (Mean) pts per study
Cardiovascular	7	15	2.1	1466	209	97
Central Nervous System	7	19	2.7	3383	483	178
Endocrine-Metabolic	10	17	1.7	2140	214	126
Gastrointestinal	3	8	2.7	1537	512	192
Genitourinary	1	7	7	815	815	116
Hematology	3	3	1	85	28	28
Immunologic	8	22	2.8	2429	303	110
Infectious Disease	9	35	3.9	5323	625	152
Oncology	9	28	3.1	1205	134	43
Ophthalmology	5	6	1.2	1169	234	195
Psychiatric-Behavioral	8	27	3.4	4022	502	149
Pulmonary	3	7	2.3	1090	363	156

Disease categories with the greatest number of studies per product were genitourinary, infectious diseases, psychiatric-behavioral and oncology. The greatest number of patients per product was in genitourinary, infectious diseases, gastrointestinal, and psychiatric-behavioral. The greatest number of patients per study was in ophthalmology, gastrointestinal, central nervous system, pulmonary and infectious diseases.

Summary:

- The incentive program has resulted in label changes to at least 118 products.
- Based on a sample of 73 products, about 80% of products granted an incentive have a label change. There was no difference in number of studies, number of patients or disease class between products that had a labeling change and those that did not.
- Of responses to pediatric Written Requests submitted to the Food and Drug Administration for a determination, about 90% are granted the incentive.
- The combined pediatric programs (incentive plus mandate) have resulted in label changes in at least 173 products.
- The resource expectations with regard to number of studies and number of patients to qualify for a pediatric incentive vary with the type of disease.
- The youngest children in general are studied the least, but all age groups are represented.