

An Electronic Strategy for Implementing a New Paradigm in Pediatric Drug Development

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Objectives

- Provide historical framework and overview of recent legislation
- Detail issues in pediatric drug development
- Describe new paradigm for pediatric drug development
- Underscore critical role of electronic communication

“Safety and efficacy in pediatric patients has not been established”

-Zosyn package insert

Historically, pediatric dosing regimens have been based on extrapolation of information from adults or on years of piece-meal investigation in children – this process is being repeated early on pediatric drug development process.

Chloramphenicol Disaster

- 1949: Chloramphenicol introduced into U.S. market
- 1958: Chloramphenicol “intoxication” first recognized and reported to Parke-Davis
- 1959, January: First published reports of death associated with “moderately large amounts”
- 1959, December: Conclusive evidence of ‘gray syndrome’ secondary to then recommended dose of chloramphenicol
- 1960-present: Despite new dosing guidelines, Chloramphenicol rarely used in developed countries

Pediatric Labeling

- 1973 PDR - 78% had insufficient pediatric information
- 1988 US hospital survey - 70% of drugs used in infants lacked pediatric labeling
- 1991 PDR - 62% were unapproved, 81% disclaimed use or restricted use to certain age groups.

Gilman JT, Gal P. *Clin Pharmacokinetics* 1992;23:1-9.

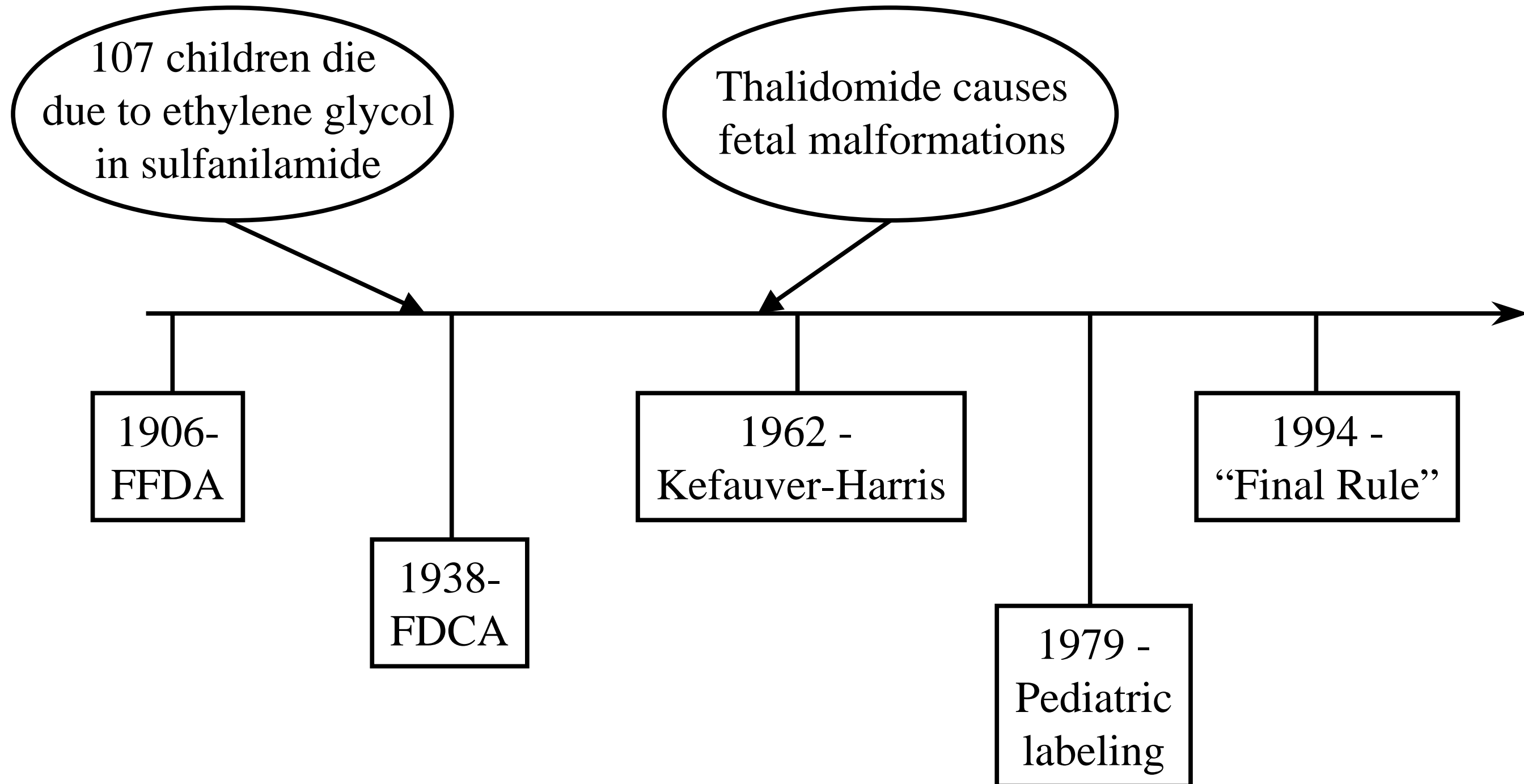
Pediatrician's Dilemma

- Withhold potentially valuable therapy due to lack of adequate studies

OR

- Put the patient at risk (and open yourself up to litigation) by using an approved drug for an unapproved indication

History of the FDCA



FDA Modernization Act of 1997

- Section 111 of the FDAMA of 1997 created section 505A of the FDCA
- Six (6) months exclusivity if “sponsor submits requested information relating to the use of the active moiety in the pediatric population.”

FDA. Guidance for Industry. Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act. September 1999.

Pediatric “Rule”

- Modification of 21 CFR Parts 201, 312, 314, and 601
- Effective April 1, 1999
- Provides FDA with the authority to:
 - Require conduct of pediatric studies
 - Require development of new formulations
- Applicable to new and old drugs
- “Appropriate regulatory actions” may be taken in cases of non-compliance
- No “off-label” requirements

Interaction of FDAMA and “Rule”

- Satisfying the “Rule” is not optional
- Exclusivity requirements are more detailed
- Exclusivity requirements may include the study of off-label indications
- Pharmacokinetic studies are critical to satisfying either one

Pediatric Drug Development

Current Process

- Pre-clinical studies
- Phase II studies in adults completed
- Phase I studies
- FDA 'guidance'
- Phase II/III studies

Pediatric Drug Development

Issues

- Ethical considerations
- Enrollment issues
- Investigator Pool
- Initial dose determination

Ethical Issues

- Informed consent vs. assent
- Perceived benefits of participation
- Lag times in reviewing safety data
- Relatively little info gleaned due to study design

Enrollment Issues

- See Ethics
- Restrictive Entry Criteria
- Patient/Parent Cooperation
- Phlebotomy/blood volume issues
- Developmental issues in a heterogeneous population

Limited Investigator Pool

- Study Sites
 - Availability
 - Facilities
- Investigator Experience
- Institutional Review Boards

Initial Dose Determinations

- Pharmacokinetic Differences
 - Animal Models
 - Allometric Scaling
 - PK/PD Modeling
- Disease Process Differences

Pharmacokinetic Differences:

Kids are not little adults

- Drug absorption
- Protein binding of drugs
- Distribution
- Clearance (renal and hepatic)
- Pharmacodynamics

Pediatric Indinavir Trial

- Study dose extrapolated from adults
- No previous data in children
- Dose adjusted based on plasma indinavir concentration
- Concluded that the indinavir dose being used in pediatric clinical trials was inadequate in 72% of patients.

Issues in Pediatric Drug Development

Recap

- Phase I trials are too expensive and provide too little information
- Enrolling pediatric patients in clinical trials is very difficult
- Current data collection/analysis methods cause lag in safety review

A New Paradigm for Pediatric Drug Development

- Avoid Phase I studies in children and move directly to Phase II
- Bolster enrollment by loosening entry criteria
- Design appropriate studies to maximize information gained
- Decrease lag time to safety review using secure internet communication

New Paradigm

Implementation

- Population Pharmacokinetic/
Pharmacodynamic analysis, Real-Time
Data Analysis, and Electronic
Communication via Virtual Private
Networks can be used to assure safety
and better define PK/PD relationships
in children through Phase II/III studies.

Population Pharmacokinetics

- Def'n: The study of the sources and correlates of variability in plasma drug concentrations between individuals representative of those in whom the drug will be clinically used.
- Seeks to discover which measurable pathophysiologic factors cause changes in the dose-concentration relationship and to what degree, so the appropriate dosage can be recommended.

Population Pharmacokinetics

- Variability in PK can make dose a poor measure of systemic exposure.
- Information on individual systemic exposure is important in the evaluation of adverse events, exaggerated drug effect, and lack of response.
- Can increase efficiency and specificity of drug development by suggesting more informative designs and analyses.

Population Pharmacokinetics

- Usually performed during Phase II/III trials
- Large, more diverse *patient* population
- Dosing is NOT generally monitored and may vary
- Sampling times not strictly scheduled and may vary across patients
- Relatively few samples obtained per patient
- Much “messier” data

Population Pharmacokinetics

Critical Data

- Drug dosing dates and times
- Drug concentration sampling dates and times
- Drug concentrations
- Patient demographic data

Population Pharmacokinetics

Application

- Optimal Sampling Theory
- Mesh known adult PK/PD with knowledge of ontogeny of drug clearance to obtain a “best guess” dosage regimen
- “Continuous” analysis allows for dosing adjustment to maximize safety

Real-Time Data Assembly

Overview

- Structured process for the rapid retrieval, assembly, and analysis of data.
- When coupled with electronic communication, provides for the rapid feedback of analysis to the sponsor and independent monitors
- Helps assure quality of data as well as continuous monitoring of safety

Real-Time Data Assembly

Overview

- Data received from the sponsor and any CROs on a regular basis
- QA procedures initiated, feedback provided
- Data entered into warehouse
- Analysis performed at regular intervals and reported as appropriate

Real-Time Data Assembly

Benefits

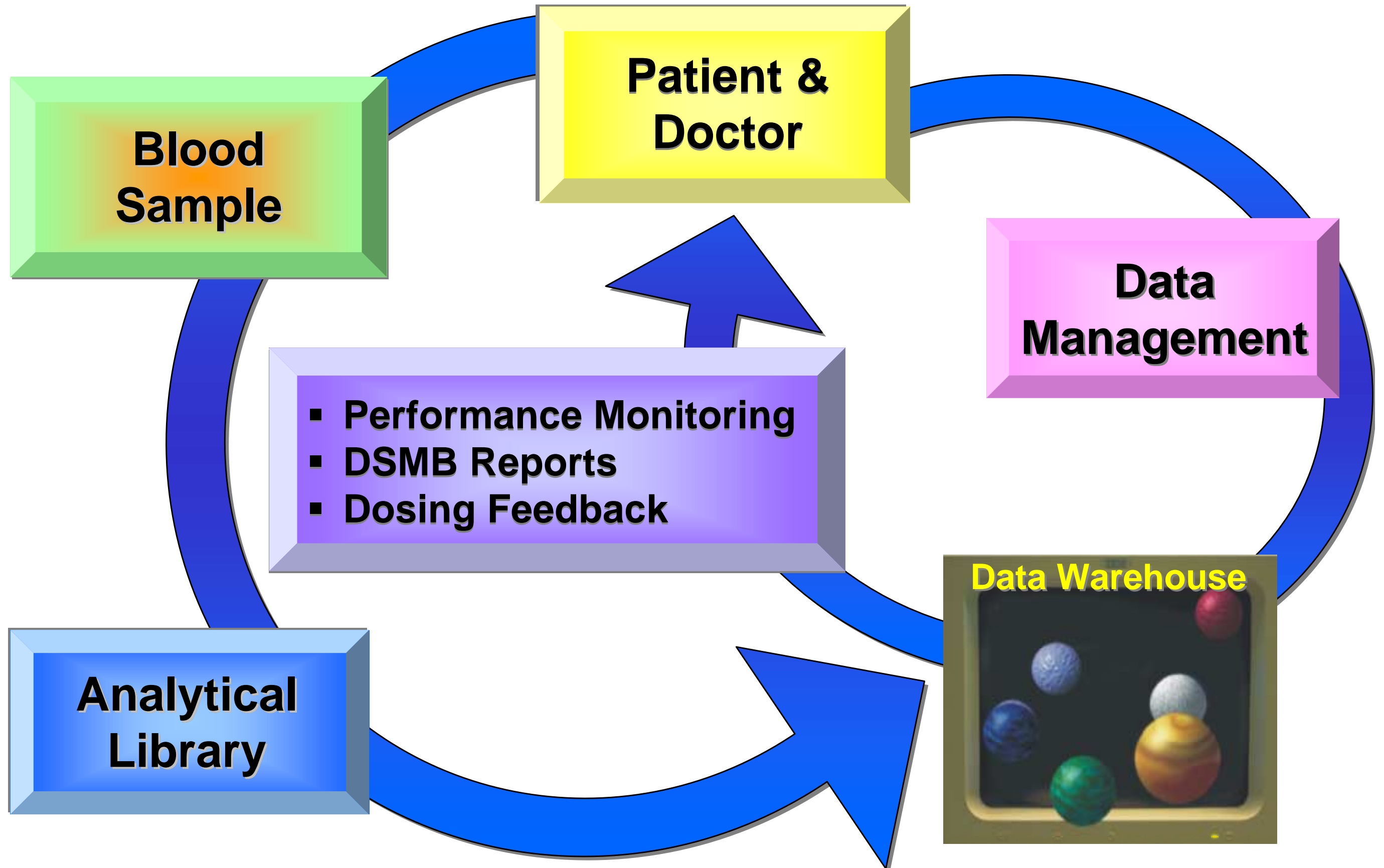
- In addition to financial and quality benefits, RTDA allows for:
 - Continuous safety monitoring which alleviates fears of over/under dosing while avoiding Phase I studies
 - An improved strategy for inclusion and exclusion of patients which enhances recruitment without sacrificing safety.

Web-Based Real-Time Data Capture

Advantages

- Makes RTDA seamless and nearly instantaneous
 - Data quality
 - Analysis time
- Helps overcome many of the logistical issues associated with population PK/PD studies
 - Investigator acceptance
 - Site monitoring
- Allows for on-line report “wizards”

Web-Based Real-Time Data Capture



▫HTML Pages used
▫by Investigational Site

▫Input
▫Patient
▫Information

▫D/E validations

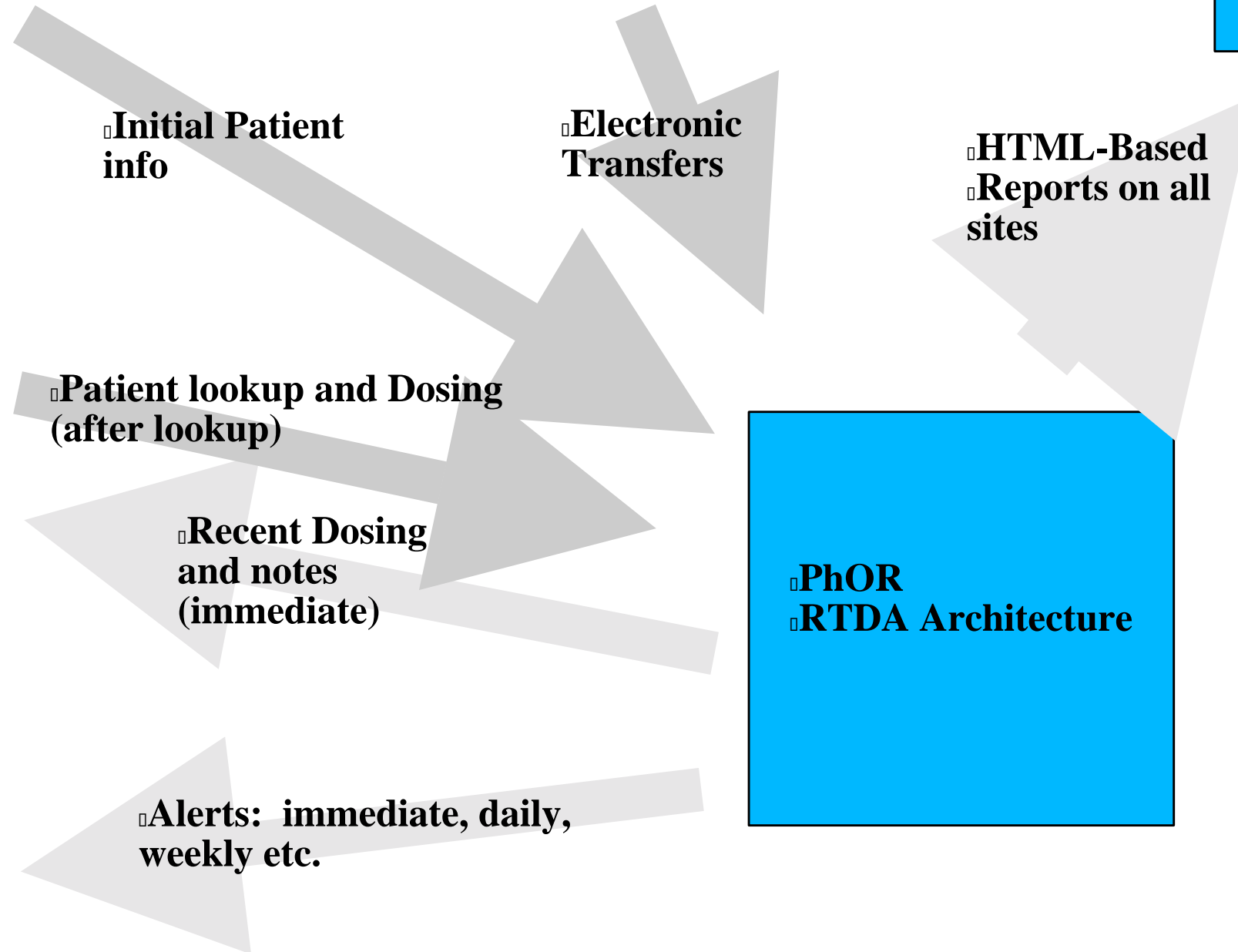
▫Input
▫Dosing and
▫Sample Times
▫for existing
▫Patient

▫D/E validations

▫Alerts to
▫site

▫Laboratories

▫Sponsor



Real-Time Data Capture Overview

Virtual Private Network

- Secure, password-protected web site
- Provides the ability to organize, summarize, synthesize, and communicate:
 - Data and graphics
 - Results and conclusions
 - Questions and action plans

Virtual Private Network

Functionality

- Project collaboration and virtual meetings
- Interactive whiteboard
- Web-based conferencing
- Discussion forums
- Sensitive document repository
- Search engine

Wrap-up

- Recent legislation has provided an opportunity to improve the pediatric drug development process.
- Advantages of population PK/PD analysis and RTDA should be exploited in that process.
- The use of innovative solutions for electronic data capture and rapid communication is critical to success.