American Academy of Pediatrics Meeting: Section on Clinical Pharmacology and Therapeutics Program

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Overview

- Background on Pediatric Drug Studies.
- You cannot copy what is not there.
- How does the generic process differ?
- Why do I need to know about this?
What I Might Learn

- Why you need to know about pediatric product development
- How to obtain the latest information on pediatric therapeutics
- What to look for on a generic label
- How a generic drug might differ from the originator drug and how it will be the same
HISTORY LESSONS

- Products should be safely manufactured
- Products should tell you what is in them
- Products should not harm you
- Products should do what they say they will do
- Products to be used in children should be studied in children. (Not Bioequivalence)
FDA and Pediatric Health

- Crises which involved children, resulted in laws benefitting adults
- Information on use of therapeutics in children remained inadequate
- Finally, in the late part of the 20th century, laws were passed to specifically address drug use in children
History of USA Pediatric Regulations/Legislation

- FDAMA Pediatric Exclusivity (incentive for sponsor) 1997
- Pediatric Rule Regulation (requirement) 1998
  (enjoined 2002 by court-FDA not have authority)
- January 2002: FDAMA Exclusivity Sunsets
- January 2002: (BPCA)
  - Best Pharmaceuticals for Children Act (incentive)
- December 2003: (PREA)
  - Pediatric Research Equity Act (requirement)
- October 2007: Sunset for BPCA & PREA
- September 2007: Food & Drug Administration Amendments Act (FDAAA) –now includes Devices
How a Drug Product might be studied in the pediatric population

- **Incentive Program** (BPCA = Exclusivity, On-patent)
  - Written Request Process (if sponsor accepts)
  - Declined WR’s can be sent to NIH

- **Requirement Program** (PREA-adult indication)

- “Off-patent” or **generic process** (List and contracting process coordinated by NICHD)

- **Orphans Program**

- None of the above: usually for product to treat pediatric disease or condition.
What This Means for You

- There is now legislation in Europe which is similar to the US legislation. This legislation means there are going to continue to be more pediatric therapeutic trials.

- There are going to be more labels with NEW PEDIATRIC INFORMATION.

- NICHD is focusing on Translational research and has funding for this type of research, including generic products.

- There is now legislation to encourage development of pediatric devices, including $2 million in FDA funding.
Pediatric Legislative Accomplishments: June 1998-September 2009

- FDA Requests for studies: N= 372
- Products with new labeling: N= 355

Breakout of Labeling changes for 355:
- Expanded age: n= 258
- Safety and efficacy not established: n= 57
- New/enhanced safety information: n= 64
- Specific dosing change/adjustment: n= 31
- Pediatric formulation: n= 23
- PK differences (pediatrics vs. adults): n= 7
US: 10 years: Where are we?

- Approximately 50% of products used in the pediatric population have had SOME subset of the pediatric population studied for some indication. (early data)
  - Over 335 products now have some pediatric information in the label
  - Specific Dosing Change/adjustment – 31
  - S&E Not Established in Pediatrics – 57
  - New or Enhanced Safety Information – 64

- Development for 57 of 335 product failed to demonstrate efficacy- usually no further development for individual product to determine why or answer evolved questions. *Dose finding needs to establish the dose for the trial.*

- Neonates remain mostly unstudied

- Ethical issues (examples): healthy children participation in trials, pre-clinical data relevance when no adult model, scientific rigor of trials.

- Size of trials for safety assessments remain small and post marketing passive reporting remains an issue.

- Device Product development is where we were in 1990’s
Areas of Ongoing Need for Research

- Neonates
- Devices
- Endpoints
- Apparent increase in pediatric for CNS adverse events for all types of products
- Basic physiology of responses that may be causing us to not assess the correct endpoint
Recent data indicate that more children in the United States are taking prescription medications and that the annual percentage increase in spending on drugs is greater for children than for adults.

NO Labeling for Pediatrics = NO generics

- You cannot copy something that does not have an original
- If the innovator product (reference labeled drug) did not have a pediatric indication the generic will NOT have any information for pediatrics
- Therefore, the major problem still exists of getting products studied in children
- There is a program at NIH for getting off-patent products, or products industry has declined to study after a Written Request from FDA, studied but we are still waiting for our first pediatric label from that program
- Thus, we really need to get the products studied while they have patent or exclusivity rights
Assuming we have a pediatric indication in the innovator product

- The generic product will have the same indication and information on pediatrics.
- A generic product may not be developed for all the dosing forms that the originator developed.
- The generic product may have different excipients.
- The generic product may not taste the same if there are different excipients.
The approved reference drug is already known to be safe and effective. The generic is the same drug in a similar formulation. Safety and effectiveness do not need to be demonstrated again. The focus is on showing bioequivalence and pharmaceutical equivalence.
## NDA vs. ANDA Review Process

<table>
<thead>
<tr>
<th>Brand Name Drug NDA Requirements</th>
<th>Generic Drug ANDA Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chemistry</td>
<td>1. Chemistry</td>
</tr>
<tr>
<td>3. Controls</td>
<td>3. Controls</td>
</tr>
<tr>
<td>4. Labeling</td>
<td>4. Labeling</td>
</tr>
<tr>
<td>5. Testing</td>
<td>5. Testing</td>
</tr>
<tr>
<td>7. Clinical Studies</td>
<td></td>
</tr>
<tr>
<td>8. Bioavailability</td>
<td></td>
</tr>
</tbody>
</table>
### Generic Drug Review Process

**APPLICANT**

**ANDA**

- Application Review

- Acceptable & Complete

- Request for Plant Inspection
- Chemistry & Micro Review
- Labeling Review
- Bioequivalence Review

- PreApproval Inspection Results OK?
- Chem/Micro OK?
- Labeling OK?
- Bioequivalence OK?

- Approval Withheld until Results Satisfactory
- Not Approvable Letter
- Bio Deficiency Letter

- Approved ANDA
- Refuse to Receive Letter

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**APPROVED ANDA**
Manufacturing Compliance Programs

Purpose - To assure quality of marketed drug products

Mechanisms - Product Testing
– Surveillance
– Manufacturing/Testing Site Inspections (EERs)
– Assess firm’s compliance with good manufacturing/laboratory processes
Chemistry Review

- Components and Composition
- Manufacturing and Controls
- Batch Formulation and Records
- Description of Facilities
- Specifications and Tests
- Packaging
- Stability
Labeling Review

- “Same” as brand name labeling
- May delete portions of labeling protected by patents or exclusivity
- May differ in excipients, PK data and How Supplied
Definition of Bioequivalence (BE)

The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Definition from 21 CFR § 320.1
Approaches to Determining Bioequivalence (21 CFR 320.24)

- In vivo measurement of active moiety or moieties in biologic fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA
Methods to Establish BE

In vivo measurements of active moiety or moieties in biological fluid

- **Rate** is measured by **Cmax**
  - Cmax is the maximum observed concentration
  - Cmax tends to have higher variability
  - Measurements should be based on adequate sampling time-points
Methods to Establish BE

In vivo measurements of active moiety or moieties in biological fluid

- **Extent of Absorption** is measured by the Area Under Curve (AUC)
  - AUC_t is a measure of the total exposure of drug to the body from time zero to the last sampling time t, where t is the last time point with measurable concentration for individual formulation.
  - AUC_{0-inf} is a theoretical measure of the total exposure of drug to the body from time zero to time infinity (AUC_{0-inf}).
Therapeutic Equivalence

Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions.
Purpose of BE Review

- Therapeutic equivalence (TE)
- Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
- The most efficient method of assuring TE is to assure that the formulations perform in an equivalent manner
Regulatory Requirements

**NDA**
- Adequate and well-controlled studies to demonstrate safety and efficacy
- Studies usually done under IND

**ANDA**
- Same active drug substance in same amount as approved reference product
- Acceptable inactive ingredients
- Bioequivalent to RLD
- Same label as RLD
- No pre-review of data
Inactive Ingredients

- If not the same as the RLD, need information to ensure that it will not change the safety and/or efficacy of the product.
- Usually acceptable if it has previously been used in another drug product for the same route of administration and in the same or higher daily amount.
Generic Considerations

- It is not fair to deny approval of a generic drug because the RLD has marginal safety or efficacy.
- We cannot hold a generic to a higher standard than the RLD.
- Safety and effectiveness have already been shown for the RLD. The generic has to meet bioequivalence criteria.
So Where are we now?
If your patient is not seeming to have the same response to a generic therapy, what should you consider?

1\textsuperscript{st}: Did the patient get what you ordered?

2\textsuperscript{nd}: Has anything else changed: other meds, new care giver, new diet?

3\textsuperscript{rd}: Are other tests appropriate?

4\textsuperscript{th}: Is switching back helpful?
What are Generic Drugs?

A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies. Even more billions are saved when hospitals use generics.
OGD Website

combination product. If FDA determines that the drug is suitable for a generic product, the petition is approved, if it is not suitable, the petition is denied.

Organization and Contact Information

- Chemistry Review Teams for Drug Therapeutic Categories
- Office of Generic Drugs Telephone Directory

Freedom of Information

- The Freedom of Information web page provides access to information from advisory committees; clinical investigators; the Division of Drug Marketing, Advertising and Communications correspondence; drug approval packages; and warning letters.

How to Contact Us

We ask you to take time to communicate with CDER about this website. What information is and isn't useful to you? Are there any additional items or categories of information you would like us to add? Please e-mail Timothy W. Ames, timothy.ames@fda.hhs.gov with feedback about this site.

* PDF requires the free Adobe Acrobat Reader
Office of Generic Drugs
Phone Directory

Immediate Office
Division of Labeling and Program Support
Division of Chemistry I
Division of Chemistry II
Division of Chemistry III
Division of Bioequivalence

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Recognition: Whose slides I have lifted and minds I have picked

- Dr. Dena Hixon
- Robert West, M.S., R.Ph
- Timothy Ames, R.Ph, M.P.H.
- Dr. Gary Buehler

All of the above individuals are in the Office of Generic Drugs within the Center for Drugs at FDA.
Science & Research

Home > Science & Research > Science and Research Special Topics > Pediatrics

Science and Research Special Topics

- Pediatrics
  - Ethics
  - Pediatric Safety
  - Scientific Activities
  - International Collaborations
  - Publications

Resources for You

- Pediatric Drug Development
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program
- Pediatric Medical Devices
- MedSun: Medical Product Safety Network
- Vaccines, Blood & Biologics

Pediatrics

New Pediatric Information in Labeling (PDF - 1428 KB)
Safety Reporting Updates
Pediatric Studies Characteristics from 2007 (PDF - 659 KB)

Ethics

Provides information on ethical issues raised in the development and use of FDA-regulated products in infants, children, and adolescents.

Safety

Resource for pediatric safety information related to drugs, biologics, and devices

Scientific Activities

Spotlight

- Safety Concerns About Testosterone Gel
- AAP News FDA Update
- NIH Children and Clinical Studies

Related Links

- Children’s Oncology Group
- American Academy of Pediatrics
- Glaser Pediatric Research Network
- European Medicines Agency (EMEA)
- HHS for Kids
- Bill and Melinda Gates Foundation
- Get Email Updates