Extrapolation of Efficacy in the Pediatric Population

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Overview

- Historical Reasons for Extrapolation
- FDA’s proposed criteria
- Review of 10 years of studies
- Confusion and “mis-use” vs. different meaning
Fundamental Challenge for pediatric drug development

- relatively small pediatric patient population available for clinical trials

- need for robust and interpretable studies
1. Background- **1992/1994**: Revision of “Pediatric Use” subsection in the Labeling= Pediatric Labeling Regulation

Drug manufacturers’ failure to provide more information about pediatric use in prescription drug labeling is due in part to the generally held impressions that the existing regulation requires that pediatric claims always be based on adequate and well-controlled studies in *children*. 
A. FDA Initiatives- 1992 (cont’d)

This proposal is one of a number of initiatives FDA has taken to encourage sponsors to study prescription drugs in children and to stimulate development of sufficient information for labeling to allow the safe and effective use of drugs in children.
B. Description of the Proposed Rule

Underlying both the existing and proposed pediatric labeling requirements is the principle that pediatric indications and labeling statements about use of a drug in children be supported by adequate scientific data.
B. Description of the Proposed Rule

Perhaps the most significant difference between the proposed rule and the current regulation is contained in proposed 201.57(f)(9)(iii). This proposed section recognizes an alternative way to conclude that there is substantial evidence of effectiveness in children for drugs already approved for the same use in adults.
"A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug’s effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted"
Different words but same message in 1998 Pediatric Rule

Background on extrapolation also discussed in preamble to 1998 Pediatric Rule Regulation where it makes it clear that safety is not to be “extrapolated”
1998 Pediatric Rule Preamble

The response to the 1994 rule has not substantially addressed the lack of adequate pediatric use information for marketed drugs and biological products. Pediatric labeling supplements were submitted for approximately 430 drugs and biologics, a small fraction of the thousands of prescription drug and biological products on the market. Of the supplements submitted, approximately 75 percent did not significantly improve pediatric use information.

Over half of the total supplements submitted simply requested the addition of the statement ``Safety and effectiveness in pediatric patients have not been established."

Note from Presenter:
(The point being that the offer of Extrapolation was not making a big impact. There could be many historical reasons why.)
1998: Pediatric Rule

Where the course of the disease and the product’s effects are similar in adults and pediatric patients, FDA may conclude that pediatric safety and effectiveness can be supported by effectiveness data in adults together with additional data, such as dosing, pharmacokinetic, and safety data in pediatric patients.
20th Century Efforts to Encourage Pediatric Studies

- 1992: Proposed Reg-Pediatric Use Subsection introduces concept of Extrapolation
- 1994: Final Reg: Peds Labeling Rule includes Extrapolation
- 1997: Exclusivity – does not discuss extrapolation
- 2001: Court enjoins FDA’s Pediatric Rule
- 2002: BPCA – not discuss extrapolation
- 2003: PREA – re-introduces Extrapolation but not as clearly
- 2007: Both BPCA and PREA are renewed for 5 years
- 2012 – BPCA and PREA “made permanent”
Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another.”
Irrespective of Source: Extrapolation of efficacy is based on evidence-based assumptions.

1) Is the course of the disease sufficiently similar in adults and children?
2) Is the response to treatment sufficiently similar in adults and children?
3) Do adults and children have a sufficiently similar exposure-response relationship OR the pediatric dose to match the adult exposure can be determined when certainty already exists on response?
Pharmacokinetic Studies

Adult pharmacokinetic data should be available to inform the pediatric pk studies.

Modeling may be helpful to determine the range of doses for the peds pk studies.

Pharmacokinetic studies should be conducted in pediatric patients with the disease of interest.
Dosing Studies

Include:

- Pharmacokinetic studies
- Exposure/ Response studies

Conducted in a sufficient number of patients in all the age ranges of pediatric patients likely to receive the medicinal product
Types of Studies-PK/PD

An approach based only on PK is likely to be insufficient when blood levels are known or expected not to correspond with efficacy or when there is concern that concentration-response relationships vary with age—NEED studies of clinical or pharmacological effects.

If the comparability of the disease and outcome of therapy are similar, but appropriate blood levels not clear, a combined measurement PK/PD approach may be necessary.

Safety study (ies) are required in addition to PK/PD studies and must be part of the final decision.
Exposure/Response Studies

May be needed if pk cannot be assessed (topical therapy such as inhaled and dermatologic therapies)

If dose response curves are not linear
Analysis of studies for 166 products submitted in response to a Written Request by 11 therapeutic areas.

- Analgesia, anesthesia and rheumatology
- Antivirals
- Cardiorenal
- Gastroenterology
- Pulmonary and Allergy
- Neurology and Psychiatry
- Ophthalmology and anti-infectives
- Oncology
- Metabolism and endocrine
- Radiodiagnostic
- Dermatology and Dental
Methods

Each Written Request was classified according to:

- extent of extrapolation of efficacy
  - no extrapolation
  - partial extrapolation
  - complete extrapolation

- pediatric age groups studied

- extrapolation between age groups or from other data

- achievement of new or extended pediatric indication

- changes in approach over time (therapeutic indication and/or drug class)
Approaches to the use of extrapolation of efficacy from adult to the pediatric population

- **No extrapolation** — Two adequate well-controlled efficacy and safety trials in children plus pharmacokinetic data
- **Partial extrapolation** — Single adequate, well-controlled efficacy and safety trial plus pharmacokinetic data or demonstration of exposure/response in defined situations
- **Complete extrapolation** — Pharmacokinetic and safety data
# Summary of Approaches to Extrapolation

(Assessment of 166 products between 1998-2008)

<table>
<thead>
<tr>
<th>Extrapolation</th>
<th>Supportive Evidence Requested From Pediatric Studies</th>
<th>Products n/N (%)</th>
<th>New or Expanded Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Two adequate, well-controlled, efficacy and safety trials plus PK data.</td>
<td>19/166 (11)</td>
<td>7/19 (37)</td>
</tr>
<tr>
<td></td>
<td>Oncology products only: sequential approach starting with phase 1/2. Do not proceed if no evidence of response.</td>
<td>10/166 (6)</td>
<td>3/10 (30)</td>
</tr>
<tr>
<td>Partial</td>
<td>Single, adequate, well-controlled, efficacy and safety trial (powered for efficacy) plus PK data.</td>
<td>67/166 (40)</td>
<td>35/67 (52)</td>
</tr>
<tr>
<td></td>
<td>Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus PK data.</td>
<td>20/166 (12)</td>
<td>15/20 (75)</td>
</tr>
<tr>
<td></td>
<td>Single exposure-response trial (not powered for efficacy) plus PK and safety data, PK/PD and uncontrolled efficacy plus safety data, or PK/PD plus safety data.</td>
<td>26/166 (16)</td>
<td>19/26 (73)</td>
</tr>
<tr>
<td>Complete</td>
<td>PK and safety data.</td>
<td>10/166 (6)</td>
<td>9/10 (90)</td>
</tr>
<tr>
<td></td>
<td>Safety data only.</td>
<td>14/166 (8)</td>
<td>6/14 (43)</td>
</tr>
</tbody>
</table>

Adapted from Table 1: Dunne J et al. Pediatrics 2011;128;e1242.
Partial Extrapolation

- This is the majority of products
- 40% Single Adequate/Well Controlled pediatric efficacy/safety trial
- 12% Controlled/uncontrolled peds trial
- 16% Exposure/Response or pk/pd with uncontrolled efficacy
- Total: 68%
Complete or No Extrapolation

- Complete Extrapolation: 14%
- No Extrapolation: 17%

Yes, I know if you add in the Partial of 68% it adds up to 99%
Example of Conditions Where Extrapolation is Not Used

- Diseases that may appear similar in pediatric patients and adults, but underlying physiology suggests a difference—many failed trials
- Neurologic/Psychiatric conditions
  - SSRIs, antidepressants in general
General Anxiety: Extrapolation not Appropriate

- Buspirone-adult General Anxiety Disorder
- Pathophysiology symptoms same as adults
- History: continuity across age span
- Studies: 2 multi center randomized double blind placebo controlled-studies to evaluate efficacy & safety-PK open labeled doses escalation

Results: safety & effectiveness not established in patients 6-17 years-at doses recommended for use in adults-PK parameter (AUC cMax) of drug found to be equal to or higher in children and adolescents than that in adults.
Partial Extrapolation (1 trial): A successful Experience

- Gabapentin - epilepsy/partial seizures
- Pathophysiology - clinical and symptom markers used for diagnosis for ages
- **History** - continuity across age span
- **Response** - Improvement in same clinical signs and symptoms as used for diagnosis
- **Studies** - double blind randomized placebo controlled, parallel group efficacy and safety study as add on therapy- population PK, open label extension, single dose PK
Partial Extrapolation (continued)

Results - Safety and effectiveness were determined in children down to 3 years of age. Neuropsychiatric AE’s were identified in 3-12 yr old. Oral clearance (normalized by body weight) increased in children < 5 yrs., thus, higher doses are required in children < 5 yrs of age.
Complete Extrapolation may be applied Without Additional Information

- Usually requires PK and safety
- Pediatric Sinusitis
  - If efficacy has been demonstrated in adult sinusitis, and if the drug is approved for the treatment of otitis media in the pediatric population, then it may be approved for the treatment of pediatric sinusitis without additional efficacy studies
Safety Studies

Safety from adults may provide some information, but it is not definitive for pediatric population.

Safety must be assessed in pediatric population with condition of interest.

May be able to utilize safety from similar pediatric indication in similar population (e.g. otitis media, sinusitis).
Changes Over Time

- Products moved from no extrapolation to some
- Products moved from extrapolation to no extrapolation
- This is a fluid process where both the experiences and new science inform it
Conclusions

Extrapolation of efficacy from the adult to the pediatric population has helped to maximize the use of existing information to increase the efficiency of pediatric drug development programs while maintaining the goal of increasing the number of safe and effective medicines approved for pediatric use based on scientifically robust data.

Over the last decade, FDA has tested its assumptions about extrapolation and modified its approaches as knowledge and experience increased. The approaches range along a continuum and are still being refined. The data presented should lead to a more informed use of extrapolation of efficacy in pediatric drug development programs for those involved in pediatric trial design as well as health professionals.
Summary

Extrapolating efficacy from adult (or other) data to the pediatric population can streamline pediatric drug development and increase the number of approvals for pediatric use.

Use of adult data requires adequate and well controlled adult studies.

Partial extrapolation was the most common approach used, reflecting some uncertainty about the strength of evidence supporting the necessary assumptions.

Safety profiles may differ between populations, which precludes extrapolation of safety information.
Words: FDA’s Specific use of this word in reference to pediatric efficacy studies.

- Extrapolation is not bridging
- Extrapolation is not “interpolating”
- Extrapolation does not include safety
- Extrapolation is, by historical explanation, restricted to Efficacy.
- For Pediatrics it has this very specific meaning
Extrapolation of Adult Data and Other Data in Pediatric Drug-Development
The Details = “Supplemental Information”

Julia Dunne, William J. Rodriguez, M. Dianne Murphy, B. Nhi Beasley, et al.
Published October 24th 2011 Pediatrics: Pediatrics 2011; 128 peds.2010-3487;
Published online October 24, 2011 10.1542/peds.2010-3487): e1242

The online version of this article, along with updated information and services, located on the World Wide Web at:

http://pediatrics.aappublications.org/content/128/5/e1242.full.html

DOI: 10.1542/peds.2010-3487
Once in the article there are notes for Supplemental Information = the data!
## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPCA</td>
<td>Best Pharmaceuticals for Children Act</td>
</tr>
<tr>
<td>FDAAA</td>
<td>Food &amp; Drug Administration Amendments Act</td>
</tr>
<tr>
<td>FDAMA</td>
<td>Food &amp; Drug Administration Modernization Act Pediatric</td>
</tr>
<tr>
<td>FDASIA</td>
<td>Food and Drug Safety and Innovation Act</td>
</tr>
</tbody>
</table>
| Pediatric Rule | The 1998 “Requirement”  
               | The 1992/94 “Pediatric Labeling” |
| PeRC    | Pediatric Review Committee |
| PREA    | Pediatric Research Equity Act |
Interpolate

To insert or introduce between other elements or parts.

Wikipedia:

In the **mathematical** field of **numerical analysis**, **interpolation** is a method of constructing new data points within the range of a **discrete set** of known data points.

In **engineering** and **science**, one often has a number of data points, obtained by **sampling** or **experimentation**, which represent the values of a function for a limited number of values of the independent variable. It is often required to **interpolate** (i.e. estimate) the value of that function for an intermediate value of the independent variable. This may be achieved by **curve fitting** or **regression analysis**.

A different problem which is closely related to interpolation is the approximation of a complicated function by a simple function. Suppose the formula for some given function is known, but too complex to evaluate efficiently. A few known data points from the original function can be used to create an interpolation based on a simpler function. Of course, when a simple function is used to estimate data points from the original, interpolation errors are usually present; however, depending on the problem domain and the interpolation method used, the gain in simplicity may be of greater value than the resultant loss in accuracy.
### Summary of approaches: Extrapolation Not Possible

<table>
<thead>
<tr>
<th>Extrapolation of efficacy from adults or other sources</th>
<th>Purpose of pediatric studies</th>
<th>Supportive evidence requested from pediatric studies</th>
<th>Products issued written requests</th>
<th>New or expanded pediatric indication achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No extrapolation</strong></td>
<td>Demonstration of efficacy and assessment of safety</td>
<td>Two adequate well-controlled efficacy and safety trials plus pharmacokinetic data</td>
<td>19/166 (11%)</td>
<td>7/19 (37%)</td>
</tr>
<tr>
<td></td>
<td>Demonstration of response and assessment of safety</td>
<td>Sequential approach starting with phase I/II. Do not proceed if no evidence of response. <em>(Oncology products)</em></td>
<td>10/166 (6%)</td>
<td>3/10 (30%)</td>
</tr>
</tbody>
</table>
Examples of “may not be appropriate for extrapolation”

- Neurotropic Bladder syndromes
- Unique epileptic syndromes
  - Examples: Neonatal seizures
    - Infantile spasms
    - Febrile seizures

Some antiepileptic drugs effective in adults may be ineffective or proconvulsant in children.

ex: carbamazepine may exacerbate certain types of pediatric seizures and vigabatrin may exacerbate myoclonic seizures in pediatrics.
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</thead>
<tbody>
<tr>
<td>Partial extrapolation</td>
<td>Confirmation of efficacy and assessment of safety</td>
<td>Single adequate, well-controlled efficacy and safety trial plus pharmacokinetic data</td>
<td>67/166 (40%)</td>
<td>35/67 (52%)</td>
</tr>
<tr>
<td></td>
<td>Confirmation of response and assessment of safety</td>
<td>Single controlled or uncontrolled efficacy and safety trial (qualitative data) plus pharmacokinetic data</td>
<td>20/166 (12%)</td>
<td>15/20 (75%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single dose or exposure-response trial (not powered for efficacy) plus pharmacokinetic and safety data</td>
<td>26/166 (16%)</td>
<td>19/26 (73%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharmacokinetic/pharmacodynamic study +/- uncontrolled efficacy data plus safety data</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“Partial” Example

Steroid Responsive Dermatosis

Example: 1 study in peds with atopic dermatitis and 1 study in adults with psoriasis
### Summary of approaches to the use of extrapolation of efficacy from the adult to the pediatric population

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<thead>
<tr>
<th>Extrapolation of efficacy from adults or other sources</th>
<th>Purpose of pediatric studies</th>
<th>Supportive evidence requested from pediatric studies</th>
<th>Products issued written requests</th>
<th>New or expanded pediatric indication achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete extrapolation</strong></td>
<td>Exposure data to confirm age-appropriate dose and assessment of safety</td>
<td>Pharmacokinetic and safety data</td>
<td><strong>10/166</strong> (6%)</td>
<td><strong>9/10</strong> (90%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Assessment of safety data only</strong></td>
<td>Safety data</td>
<td></td>
<td><strong>14/166</strong> (8%)</td>
<td><strong>6/14</strong> (43%)</td>
</tr>
</tbody>
</table>