Selected Issues in Pediatric Clinical Trials: An “FDA” Perspective

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Disclaimer

- The views expressed in this presentation are those of the presenter and do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
- Robert Nelson has no financial conflicts of interest to disclose.
State of Pediatric Therapeutics

• Infants, children and adolescents who are in need of treatment deserve to receive medical products that have been shown to be both safe and effective in infants, children and adolescents.

• Off-label pediatric use of medical products may be necessary at times, but is an unacceptable policy.

• Various incentives to stimulate pediatric clinical trials have been put in place over the past 20 years, reducing the number of medical products that lack appropriate pediatric labeling. However, challenges remain.
Topics

• Addressing the Challenges of Pediatric Studies through the Use of Incentives
• Applying the additional safeguards for children enrolled in clinical investigations to
  – The timing of pediatric studies
  – “First-in-Children” clinical studies
  – Use of biomarkers that require procedural sedation
  – Use of “invasive” placebos
Established in 1997, and made permanent in 2012, a sponsor may receive 6 months of marketing exclusivity added to existing patents on all forms and uses of the active moiety.

To be eligible, a sponsor must conduct and submit (by an agreed deadline) the pediatric studies requested by FDA for all indications where there may be a “meaningful therapeutic benefit” in children.

FDA can expand the pediatric indications for which clinical (and nonclinical) studies are requested, creating some risk for sponsors.

Although often tied to a successful adult development program, the additional marketing exclusivity is still valuable for stand-alone pediatric development programs.

Under BPCA, NIH has the authority to conduct and submit studies to FDA in support of pediatric labeling.

† Referred to as “BPCA” (Best Pharmaceutical for Children Act)
Established in 2003, and made permanent in 2012, PREA requires that all applications (or supplements to an application) submitted for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration contain a pediatric assessment unless the assessment is either waived or deferred (in which case, the study is converted to a post-marketing requirement).

A pediatric assessment must contain data to assess the drug’s safety and effectiveness for the claimed indication in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective.

If FDA determines that the course of the disease and the effect of the drug are sufficiently similar in adults and pediatric patients, pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults (or from one pediatric subpopulation to another).

† Referred to as “PREA” (Pediatric Research Equity Act)
New Pediatric Labeling

• Since 1998, there have been 674 pediatric labeling changes as a result of the BPCA and/or PREA incentives.

• Of these,
  – 171 labeling changes were the result of studies conducted under BPCA alone;
  – 94 labeling changes in response to both BPCA and PREA;
  – 360 labeling changes in response to PREA alone; and,
  – 49 labeling changes in response to the 1998 Pediatric Rule (precursor to PREA).

Orphan Drug Exclusivity (ODE)†

• Drug must be designated and approved to treat diseases or conditions affecting less than 200,000 patients in the U.S. (or more than 200,000 and no hope of recovering costs), where either (1) no current therapy exists or (2) the product will significantly improve existing therapy.

• Following approval, bars FDA from approving any other application for the same drug for the same orphan disease or condition for seven years (Note – labeling “carve out” for ANDAs).

• Tax credits for up to 50% of clinical development costs (U.S. studies)

• User fees paid to FDA for review of the application are waived.

• Grant funding available from FDA for clinical studies that will result in or substantially contribute to market approval.

• Orphan Drugs are exempt from the requirements of PREA.

† 21 CFR Part 316: Orphan Drug Regulations - Final rule. 78 Federal Register 35117-35135 (June 12, 2013).
A “rare pediatric disease” must qualify for orphan designation and have serious or life-threatening manifestations that primarily affect individuals aged from birth to 18 years.

Upon approval of an eligible rare pediatric disease product application, the sponsor shall receive a priority review voucher.

The recipient may either use the voucher for a future application, or transfer (including by sale) the voucher to another party. Vouchers may be transferred more than once.

The applicant that uses the voucher is entitled to a priority review of its application, but must pay FDA a user fee ($2,706,000 in FY 2017) in addition to any user fee required by PDUFA for the application.

A priority review has a goal date of 6 months (versus 10 months) after the receipt or filing date, depending on the type of application.
Alliance For Childhood Cancer

- Make PREA relevant to targeted therapies (currently limited to “indication”)
- Remove PREA's orphan drug exclusion
- Encourage earlier pediatric discussion of PREA for drugs for serious or life-threatening conditions (currently required at end-of-phase 2)
- Encourage earlier pediatric discussion of BPCA for drugs for serious and life-threatening conditions and issue written requests earlier
- Develop a plan to achieve earlier submission of BPCA studies
- Improve transparency of BPCA activities in progress (through making Written Requests public upon agreement or denial by sponsor)
- Conduct continued evaluation of BPCA and PREA for pediatric cancer

Advancing Drug Development for Childhood Cancer: Policy Principles to Optimize the Pediatric Drug Laws (Updated: June 14, 2016). Note: The above recommendations are provided for information only and are not an endorsement of these legislative proposals.

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• Served as Co-Chair of the Alliance for Childhood Cancer working group and endorsed the report’s recommendations (listed on the previous slide)

• In addition, AAP supports civil monetary penalties:
  – “Currently, if PREA studies are not completed on time, FDA has two options: declaring a drug to be misbranded, which experts say is unlikely to happen; and issuing noncompliance letters that are posted on FDA’s website.”
  – “AAP believes FDA should have the ability to impose civil monetary penalties for overdue PREA studies, the same authority it has for postmarketing studies required under the FDA Amendments Act’s drug safety provisions.”

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Additional Safeguards for Children

21 CFR 50 Subpart D
(Appropriate Balance of Risk and Benefit)

• Research interventions involving children either
  – must be restricted to “minimal” risk or a “minor increase over minimal” risk absent a potential for direct benefit to the enrolled child, or
    • 21 CFR 50.51/53; 45 CFR 46.404/406
  – must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
    • 21 CFR 50.52; 45 CFR 46.405
Two Key Concepts

• Prospect of Direct Benefit
  – The risks to which a child may be exposed depend on whether the intervention does or does not offer that child a prospect of direct benefit.
  – Thus, defining and assessing the possibility of direct (clinical or therapeutic) benefit is an essential aspect of the ethical acceptability of the (interventions included in a) research protocol.

• Component Analysis
  – A protocol may (and usually does) contain multiple interventions or procedures, some that offer a prospect of direct (clinical) benefit and others that do not.
  – These interventions and procedures must be analyzed and justified separately (i.e., as “components” of the protocol).
  – Thus, a protocol may include components that must be evaluated under 21 CFR 50.52 and others that must be evaluated under 21 CFR 50.51/53.
Timing of Pediatric Studies

• For “higher risk” interventions, administration of FDA-regulated products in a clinical investigation must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
  – Additional Safeguards for Children (21 CFR 50.52/45 CFR 46.405)

• Thus, we need “proof of concept” data from human adults and/or animal disease models establishing a sufficient prospect of direct benefit to justify exposing children to the known (and unknown) risks of the intervention.

• This requirement does not imply that adult studies must be completed before beginning pediatric studies. Rather, once sufficient adult and/or animal data exist to make this judgment, pediatric development should proceed without further delay.
• Can one infer a sufficient prospect of direct benefit from animal studies alone to justify a “first-in-children” clinical trial?
  – The data necessary to establish a sufficient prospect of direct benefit (PDB) to justify the risks of product administration varies with the severity of the disease and the adequacy of alternate treatments.

• Proposal: Sliding Threshold
  – Structure (generally insufficient for PDB)
  – Function (based on mechanism of action)
    • Molecular target (receptor); Biomarker (RNA/protein); Physiologic pathway (metabolic product)
    • Transgenic Technology (human target + mouse)
  – Clinical Disease Model
    • Surrogate endpoints
    • Clinical endpoint (e.g., survival) (FDA “Animal Rule”)
Maximum Recommended Starting Dose (MRSD) for “first-in-human” clinical trials

- MRSD is frequently based on the “no observed adverse effect level” (NOAEL) in the tested animal species, with conversion of the NOAEL to a human equivalent dose with application of an additional safety factor.
- Risk/potential benefit for NOAEL “safe starting dose” may not be equivalent to MRSD dose associated with greatest efficacy in animal studies.
- A NOAEL dose may not offer a sufficient Prospect of Direct Benefit to justify a “first-in-children” clinical trial, although the MRSD may present greater risks.

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Use of Muscle Biopsies as a Biomarker in Muscular Dystrophies

• At a minimum, muscle biopsies are performed at baseline and study completion to measure effect of an experimental product.
• Other than perhaps to establish an initial diagnosis, muscle biopsies are not clinically indicated for disease management and do not offer a prospect of direct clinical benefit to the child.
• In addition, anesthesia/sedation is required for muscle biopsies.
• Thus, the muscle biopsy and anesthesia/sedation must present no more than a “minor increase over minimal risk” (21 CFR 50.53).
• Otherwise, the protocol could be referred by an IRB for federal panel review under 21 CFR 50.54.
Question 1 (non-voting):

- Please discuss the factors which should be taken into account when designing a protocol to provide procedural sedation for nontherapeutic procedures in pediatric clinical investigations.

Question Two (voting):

- Assuming the risks have been minimized, are there one or more approaches to procedural sedation that would present no more than a minor increase over minimal risk? (Yes/No)
Committee Vote and Discussion: YES: 7 NO: 9

- The Subcommittee was not able to agree on whether one or more approaches to procedural sedation would present no more than a minor increase over minimal risk.
  - Members voting yes cited the importance of limiting nontherapeutic procedural sedation to high-volume centers with highly experienced providers, and to children for whom procedural sedation would not pose elevated risks (e.g. based on ASA risk classification).
  - Members voting no commented that procedural sedation posed greater risks than those allowed under a minor increase over minimal risk category or were concerned about the likelihood that nontherapeutic procedures requiring sedation would be allowed in situations that posed greater risk to children.

March 23, 2015
The Subcommittee generally agreed that

(1) procedures should be performed at a high volume center with a dedicated pediatric sedation service;

(2) there should be rigorous scientific justification for the need for the nontherapeutic procedures;

(3) the approach to procedural sedation and risk minimization procedures should be described in the protocol;

(4) children with chronic conditions that may place them at higher risk from procedural sedation should be carefully evaluated and potentially excluded from the protocol;

March 23, 2015
The Subcommittee generally agreed that

(5) nontherapeutic procedure should be terminated if complications of sedation arise or level of sedation inadequate; inappropriate to escalate procedural sedation beyond what would be considered a minor increase over minimal risk;

(6) if a particular procedure in a patient population is normally accompanied by sedation when performed for clinical reasons, sedation should not be withheld in the nontherapeutic research setting to avoid risks and enhance procedure’s approvability; and

(7) clear communication with potential subjects (and parents) about nontherapeutic nature of procedures and procedural sedation

March 23, 2015
Source of Ongoing Controversy

- Some IRBs approve the muscle biopsy/procedural sedation under 21 CFR 50.52 (ignoring that biopsies may be performed in children randomized to a placebo and/or an untreated control), believing the procedure exceeds a minor increase over minimal risk, rather than refer for federal review under 21 CFR 50.54.
  - This approach is **not** in compliance with FDA regulations

- Dystrophin levels are not yet proven (i.e., validated) as a surrogate marker of meaningful clinical benefit, but may serve as the basis for an accelerated approval (“reasonably likely”).

- The controversy should provide us with a sense of urgency to develop alternative biomarkers that are less invasive and do not require a surgical procedure under general anesthesia.

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Choice of Control Group

- Placebo Control (i.e., masking treatment assignment)
  - Concurrent “no treatment” control (i.e., not masked)
  - May be used in “add on” trial of a new treatment compared to existing standard of care (or known effective treatment)
- Another Alternative (avoids use of placebo)
  - Dose-response design (but need separation between doses)
- Active Treatment Control
  - Non-inferiority design (based on previous placebo-controlled trials so that a non-inferiority margin can be estimated)
  - Superiority design (as is done with a placebo control)
- External Controls
  - Retrospective (or prospective) “natural history” control
Placebo (Sham) Controls in Pediatrics

• Placebos (and sham procedures) do not offer any prospect of direct benefit to the enrolled children

• Placebos present two types of risk
  – Placebo risk itself may be “minimal” unless invasive (e.g. injections)
  – Risks from withholding “proven” or “known effective” treatment

• Both types of risk must be no greater than a “minor increase over minimal risk” (21 CFR 50.53)
  – This approach consistent with ICH E-10 and 2013 Declaration of Helsinki.

• Placement of an indwelling port or central catheter (PICC) exceeds this level of risk, and thus is not approvable for children receiving placebo infusions absent referral for federal panel review under 21 CFR 50.54
Use of Clinical Hold in Pediatrics

- Criterion for a clinical hold under 21 CFR 312.42: Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.
- 21 CFR 50 subpart D sets the standards for “reasonable” risk exposure in pediatric clinical trials.
- If the risks of an intervention fall outside of these standards, the intervention exposes the enrolled child to an “unreasonable and significant risk of illness or injury.”
- Thus, failure to be in compliance with 21 CFR 50 subpart D is sufficient grounds for imposing a clinical hold on a proposed or on-going pediatric clinical trial.

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Thank you.