Pediatric Ethics Subcommittee Meeting Summary
June 9-10, 2008

Robert M. Nelson, M.D., Ph.D.
Pediatric Ethicist, Office of Pediatric Therapeutics, Food and Drug Administration

Charter - Pediatric Advisory Committee (PAC)

- The PAC advises and makes recommendations to the FDA Commissioner regarding… the ethics, design, and analysis of clinical trials related to pediatric therapeutics, and research involving children as subjects under 21 CFR 50.54 (and to the HHS Secretary under 45 CFR 46.407).
- A permanent Pediatric Ethics Subcommittee (PES) of the PAC advises and makes recommendations to the PAC on pediatric ethical issues, and IRB referrals related to clinical investigations involving children as subjects under 21 CFR 50.54 and 45 CFR 46.407.
- The PES will consist of two or more members of the PAC and additional experts (e.g., science, medicine, education, ethics and law) to address specific issues within their respective areas of expertise.

http://www.fda.gov/oc/advisory/OCPedsCharter2006.html

PES Meeting Agenda

- Overall Focus
  - Discuss the application of 21 CFR 50.52 (Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects) to FDA-regulated research.
- Monday, June 9, 2008
  - The discussion will be illustrated with hypothetical case examples of research involving HIV vaccines in adolescents (AM) and controlled trials of inhaled corticosteroids in children with asthma (PM).
- Tuesday, June 10, 2008
  - The discussion will be illustrated with a hypothetical case example of research using stem cells for treating neonatal hypoxic-ischemic injury.

3

Structure of Discussion

- For each hypothetical case description
  - Presentation of selected ethical concepts that may be pertinent to the case discussion
  - Presentation of the hypothetical case description and discussion questions
  - PES discussion of the ethical issues
- Note: Slides Edited for this Presentation.

4

First Background Presentation:
21 CFR 50, Subpart D

Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products

Robert M. Nelson, MD PhD
Pediatric Ethicist, Office of Pediatric Therapeutics, Food and Drug Administration

"Nested" Protections

Scientific Necessity

Parental Permission

Child Assent

Appropriate Balance of Risk and Benefit

Principle of Scientific Necessity

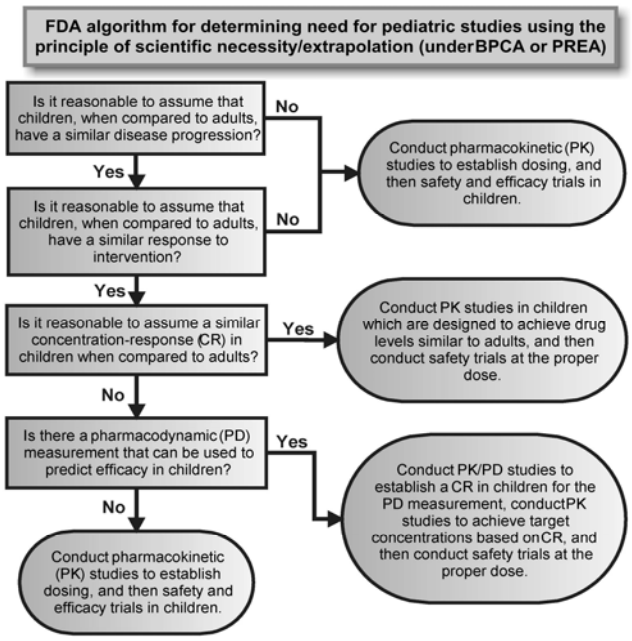
- Children should not be enrolled in a clinical investigation unless absolutely necessary to answer an important scientific question about the health and welfare of children.
  - Study design capable of answering question
    (e.g., sample size, control group, blinding, etc.)
  - Practical application: “extrapolation”
  - Objective: “public health benefit” for children

21 CFR 56: Criteria for IRB Approval of Research

- Minimize Risks [21 CFR 56.111(a)(1)]
  - Eliminate any research procedures (as unnecessary) that do not contribute to scientific objective
- Equitable selection [21 CFR 56.111(b)]
  - Subjects capable of informed consent (i.e., adults) should be enrolled prior to children
  - Do not enroll children unless essential (i.e., no other option, whether animal or adult human).

Extrapolation

- "If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary 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 PK studies."
- "A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group."



Appropriate Balance of Risk and Benefit

Adults (21 CFR 56.111)

- Risks are reasonable in relation to anticipated benefits, if any, to subjects and importance of knowledge that may reasonably be expected to result

21CFR 56.111

"Subpart D" (children)

- For research not offering the prospect of direct benefit, restricts allowable risk exposure (minimal risk, minor increase over minimal risk; ICH E6 GCP §4.8.14 "low")

21CFR 50.51 & 50.53

- For research that offers prospect of direct benefit, restricts justification of risk exposure

21CFR 50.52

11

FOCUS: 21 CFR 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

- Any clinical investigation … in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if…:
  a) The risk is justified by the anticipated benefit to the subjects;
  b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
  c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 50.55.

12

First Hypothetical Case Description:
Enrolling Adolescents in an HIV Vaccine Clinical Study

The following case description uses published information to construct a generic description of a typical clinical investigation that is not unique or specific to any particular product.

13

Proposed Clinical Trial

- A phase 2 “proof of concept” trial of a new vaccination strategy against HIV infection is being considered.
- The strategy combines three initial priming vaccinations with a DNA vaccine that incorporates selected HIV genes including envelope, followed at six months by a modified poxvirus vectored vaccine containing the same HIV genes.

14

Pre-clinical Testing

- Pre-clinical testing of this prime/boost regimen demonstrated relative protection against homologous simian immunodeficiency virus challenges in non-human primate models involving mucosal exposure.
- Although the vaccine did not prevent HIV infection, immunized animals had a reduced per-exposure probability of becoming infected as compared with controls.

15

Early phase adult human experience

- Several phase 1 clinical trials involving healthy adult volunteers demonstrated T cell responses lasting in the majority of subjects out to 12 months.
- In these adult studies, no serious adverse events were identified.
- The most common local reactions were pain and erythema at the injection site, experienced by the majority of subjects. Mild and moderate fatigue and myalgia, lasting up to four days, occurred in a minority of subjects.

16

Early phase adult human experience

- Of note, the majority of subjects also developed false-positive results from commercial HIV screening tests at the dose selected for phase 2 testing.
- Additional testing can discern false versus true positive tests for HIV infection; however, the duration that commercial screening tests for HIV remain positive is unknown.
- To date, there is no immunological surrogate that can serve as a short term marker of potential clinical benefit in reducing the incidence or mitigating the severity of HIV infection.

Proposed Endpoints

- The phase 2 clinical trial plans to enroll a sufficient number of high risk adult subjects 18 to 30 years of age to be able to evaluate
  1) whether the vaccination regimen reduces the acquisition of HIV infection (as the primary endpoint) and/or
  2) decreases the viral load at three months post-diagnosis in those subjects who become HIV infected.

Study Conduct

- The study will be conducted at multiple sites selected based on a high prevalence of HIV infection. After informed consent, subjects will be randomized equally to either active or placebo vaccination administered in a blinded fashion to minimize bias. The study duration has been estimated based on a sufficient number of HIV infections occurring in the enrolled subjects to assess the primary endpoint. Risk reduction counseling, use of post-exposure prophylaxis, and standard anti-retroviral treatments for those subjects who become HIV infected during the trial are all included in the protocol. Interim analyses are planned for safety and efficacy after half of the necessary HIV infected cases have occurred.

Question

- Please discuss the ethical considerations that should go into a decision about whether (and, if yes, when) to enroll adolescents in the above phase 2 clinical investigation.
- As part of your discussion, please address the threshold of evidence necessary to establish that the study intervention offers a sufficient prospect of direct benefit to justify the risks of vaccine administration.
  - For example, are interim or final results from adult phase 2 or 3 studies needed prior to studies in adolescents?
  - How does the lack of an immunological surrogate for clinically meaningful benefit affect the prospect of direct benefit?
- Issues you may want to consider include:
  a) the distinction between evidence sufficient to establish the prospect of direct benefit versus evidence sufficient to establish efficacy;
  b) the choice of adolescent populations (i.e., at risk); and
  c) the use of comparable adolescent immunogenicity and/or safety data as a bridge to extrapolate from adult clinical outcomes data to efficacy in the adolescent population.

Subcommittee Discussion

- The Subcommittee commented upon… factors which might impact on whether and when to enroll adolescents in clinical investigations. Starting with the importance of scientific necessity, the Subcommittee identified such factors as age, behavioral considerations, the likelihood of physiological differences, “at risk” populations, clinical trial target populations, relative efficacy across different study populations, pre-existing safety and effectiveness data, and the risk benefit analysis as important considerations.

21

Subcommittee Discussion

- The Subcommittee identified scientific necessity, extrapolation, prospect of direct benefit, risk of the intervention, the disorder or condition to be treated, and qualifying “direct benefit” as issues to evaluate in designing a clinical investigation.
- The Subcommittee agreed on the importance of studies in children when scientifically appropriate, and both patient and parental consent are important components of the enrollment process.

22

Background Presentation for Second Case:

Choice of Control Group

Robert M. Nelson, M.D., Ph.D.

Pediatric Ethicist, Office of Pediatric Therapeutics, Food and Drug Administration

Choice of Control Group

- The selection of an appropriate control group is a critical decision which impacts on the scientific validity and ethical acceptability of a clinical investigation.
- The proper control group allows for discrimination between patient outcomes caused by the test treatment, and outcomes caused by other factors such as the natural progression of the disease, observer or patient expectations, or other treatments.

Types of Control Groups

- Concurrent Control (control/test groups chosen from same population, usually by randomization, and treated concurrently)
  - Placebo (e.g., two or three-arm study)
  - Active (Positive)
  - Dose-Response (different dose or regimen of study treatment)
  - No treatment (not blinded)
- External (including historical) Controls, regardless of comparator treatment

Choice of control in clinical trials

- “As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".

Choice of control in clinical trials

- "Placebo may be used:
  - "When there is no established effective intervention;
  - "When withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;
  - "When use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects."

E-10 Choice of Control Group and Related Issues in Clinical Trials, May 2001; also CIOMS 2002

27

Component Analysis

- "To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively, as is done in clinical practice. Research protocols meeting the criteria [of 21 CFR 50.52] regarding risk and benefit may be conducted or supported provided the conditions of [21 CFR 56.111] and the requirements [of 21 CFR 50.55] will be met. If the research also includes a purely investigative procedure presenting more than minimal risk, the research should be reviewed under [21 CFR 50.53] with respect to such procedure."
  - The National Commission 1978

28

General Ethical Principles of Subpart D

- Research involving children <u>either</u> must present a balance of risks and potential benefits comparable to the available alternatives (21 CFR 50.52), <u>or</u> be restricted to “minimal (or low) risk” absent direct benefit to child (21 CFR 50.51 or 53).
- Under 21 CFR 50, Subpart D, withholding known effective treatment from children enrolled in a control group must present no more than a “minor increase over minimal risk” (21 CFR 50.53).

29

Second Hypothetical Case Description: Study of ICS in Children with Mild Persistent Asthma

The following case description uses published information to construct a generic description of a typical clinical investigation that is not unique or specific to any particular product.

30

Background

- A sponsor has developed a new inhaled corticosteroid (ICS) that may have a decreased steroid-induced effect on bone growth based on results from cell culture and animal models.
- The investigational (study) ICS has been shown to be safe and effective for the treatment of adolescents and adults (12 years of age and older) with asthma.

31

Proposed Study Objectives

- The sponsor now wants to demonstrate that the study ICS is both safe and effective for the treatment of children with asthma and minimizes the adverse effect on growth (as measured by prepubescent growth velocity).
- As part of the pediatric clinical program, the sponsor is proposing a year-long growth study.

32

Proposed Clinical Trial Design

- The proposed study is a randomized, double-blind, double-dummy, parallel group, placebo-controlled, 56-week study to evaluate the safety and efficacy of two different doses of the study ICS when administered via metered-dose inhaler (MDI) to children between 5 to 8 years of age with mild persistent asthma.
- To assure assay sensitivity, the study design also includes an approved ICS with known effects on linear growth as a positive control group.

33

Randomization

- After a placebo run-in period, children with a history of mild persistent asthma for a minimum of six months will be randomized in equal ratios to one of four treatment arms:
  - 100 µg BID of study ICS (one MDI puff);
  - 200 µg BID of study ICS (two MDI puffs);
  - 200 µg BID of the comparator ICS; or
  - matching-image placebo for each drug.
- The doses of the study ICS are chosen not to exceed the lowest dose found to be safe and effective in adolescents.

34

Subject Selection Criteria

- In addition to meeting the 2007 National Asthma Education and Prevention Program (NAEPP) criteria for mild persistent asthma (e.g., FEV1 > 80%), enrolled patients are required to be in Tanner stage I and with heights and weights in the 5th to 95th %ile range for age.
- In addition, bone age as measured by wrist radiograph should be less than 1 year different from the patient's chronological age.
- Children who used an ICS within 6 weeks and systemic corticosteroids within 3 months of the first baseline visit and during the placebo run-in period will be excluded.

Concurrent Medications

- Subjects are permitted to receive an approved leukotriene modifier whose effect on linear growth has already been well characterized, if
  1) the treatment was prescribed at least four weeks prior to the study, and
  2) the dosing regimen remains constant following randomization.
- All subjects will be allowed to use β-agonists as needed throughout the study.

Primary Endpoints

- The primary safety end point is linear growth velocity, measured using a stadiometer.
- The primary efficacy variable is the forced expiratory volume at 1 second (FEV1).

Treatment of Acute Asthma Exacerbations

- For safety reasons, standard-of-care guidelines based on the NAEPP guidelines will be followed in the management of all acute asthma exacerbations.
- Subjects are allowed up to four rescue treatments with oral corticosteroids during the trial before being converted to open-label ICS.
- In addition, any subject experiencing one episode of life-threatening asthma will also be converted to open-label ICS.
- These subjects will remain in the study for the purpose of the primary safety endpoint, and be considered a treatment failure for the primary efficacy variable.

Question One

- Please discuss the assessment of the potential benefits of this clinical investigation for the enrolled children.
- Issues you may want to consider include:
  a) whether the potential benefits would apply equally to both the intervention and control groups;
  b) the distinction between benefits that may occur as a direct result of the experimental intervention versus those that may occur from inclusion in the clinical trial independent of the experimental intervention (i.e., the so-called "inclusion" benefit); and
  c) whether any additional monitoring procedures required by the administration of the experimental product would be considered a direct benefit or evaluated as a risk that must be balanced by the potential direct benefit of the experimental product.

39

Question Two

- Please discuss the assessment of the risks of this clinical investigation for the enrolled children.
- Issues you may want to consider include:
  a) the risks of withholding the known effective ICS comparator from the two experimental ICS arms and the negative (i.e., placebo) control arm;
  b) the impact of the selection of subject population on those risks (e.g., mild or moderate persistent asthma);
  c) the role of other study modifications such as the use of other rescue and/or controller medications; and (d) the risks of any monitoring procedures made necessary by the experimental intervention.

40

Question Three

- Please discuss the analysis of this proposed trial under Subpart D.
- In your discussion, please address whether the different study arms should be evaluated together (i.e., as one cohort before randomization) or separately (i.e., as separate cohorts after randomization).
- Issues you may want to consider include: (a) the distinction between prospect of direct benefit for each arm of the clinical study and efficacy as the primary objective of the clinical study.

41

Subcommittee Discussion

- The Subcommittee discussed the prospect of direct benefit for different treatment groups and commented that both the benefit to the child and risk of the intervention are important considerations for each treatment arm in a clinical investigation.
- The Subcommittee discussed trial design, including the risk of being in a placebo group; trial impact (e.g. enrollment, management, treatment paradigm, and increased access to healthcare); and compensation, and how these factors may influence potential benefit to the subject.

42

Subcommittee Discussion

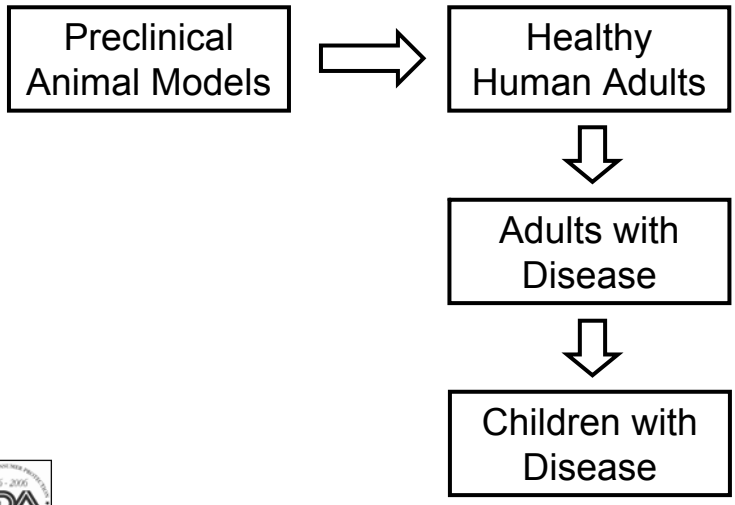
- The Subcommittee also commented upon equipoise, standard of care, and pre- and post-randomization analyses as additional components to consider when assessing potential benefits of a clinical investigation for an individual subject.

Background Presentation for Third Case:

Prospect of Direct Benefit based on Animal Studies

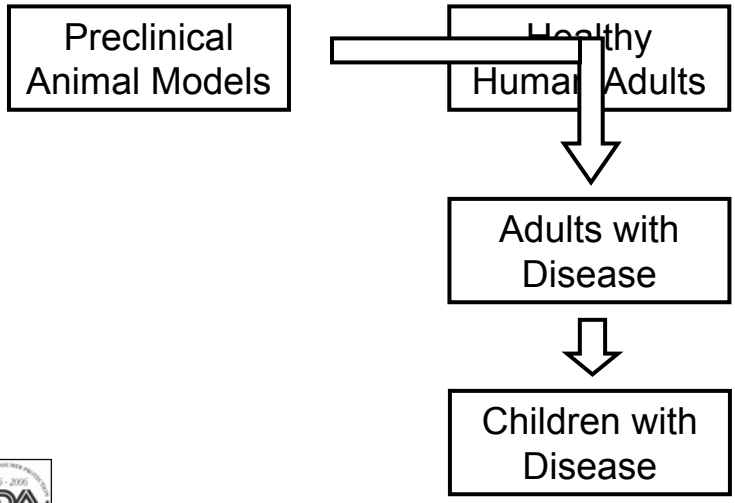
Robert M. Nelson, MD PhD
Pediatric Ethicist, Office of Pediatric Therapeutics, Food and Drug Administration

Pediatric Drug Development



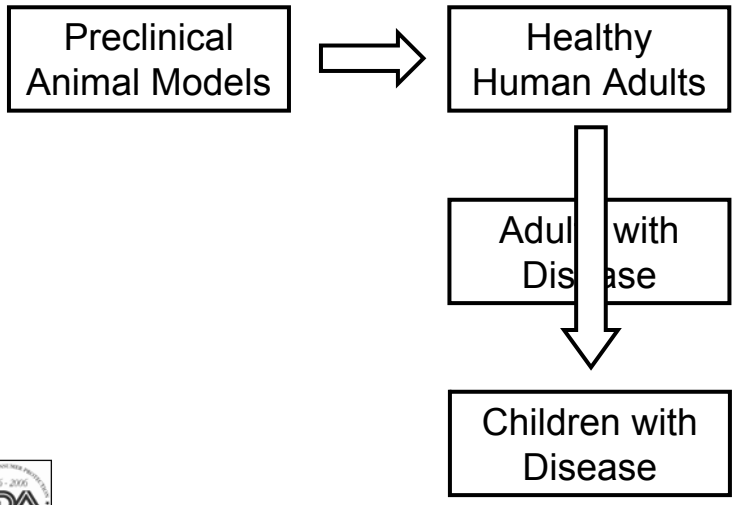
45

Pediatric Drug Development



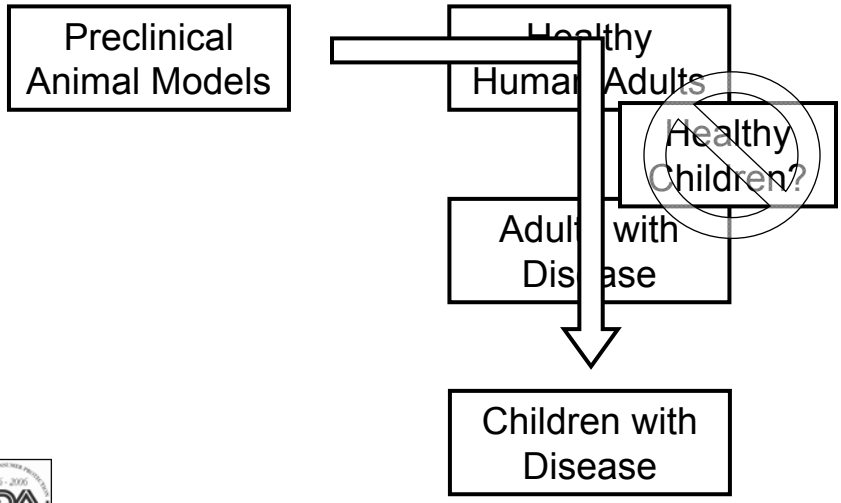
46

Pediatric Drug Development



47

Pediatric Drug Development



48

“First-in-Children” under 21 CFR 50.52

- Any clinical investigation [presenting] more than minimal risk to children… by an intervention [with] the prospect of direct benefit… may involve children as subjects only if:
  - risk justified by anticipated benefit to subjects;
  - relation of anticipated benefit to risk as favorable to subjects as… available alternative approaches.
- Absent a suitable adult human population, the challenge is to establish a sufficient prospect of direct benefit from animal studies alone to justify a “first-in-children” clinical trial.

Prospect of Direct Benefit (PDB)?

- A “benefit” is “direct” if it:
  - Accrues to individual subject enrolled in clinical trial, and
  - Results from research interventions required to answer scientific questions posed by trial (i.e., not from other interventions included in protocol, but unrelated to the research question).
  - The word “benefit” often preceded by “clinical” to indicate that “direct benefit” relates to the health status of the enrolled subject.

Prospect of Direct Benefit (PDB)?

- Based on "structure" of intervention (i.e., dose, duration, method of administration, etc.), and not an investigator's intent.
- Evidence for PDB can be "weaker" than evidence supporting "efficacy" - otherwise one needs to know the answer to the research question prior to doing the research.

51

Justification of Risk

- Need empirical evidence of sufficient "prospect of direct benefit" to justify exposure to the risks.
  - Complex quantitative and qualitative judgment
  - Risk/benefit evaluation similar to clinical practice
- Justification of risk by PDB can include:
  - Importance of "direct benefit" to subject
  - Possibility of avoiding greater harm from disease
  - Risks of experimental intervention can only be justified by benefits to be expected from that same intervention
  - Justification set in context of disease severity (e.g., degree of disability, life-threatening) and availability of alternative treatments.

52

Proposal: Sliding Threshold

- Animal data necessary to establish sufficient justification for the prospect of direct benefit (PDB) varies with the severity of the disease and the adequacy of alternate treatments.
- 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)

53

Dosing Considerations

Maximum Recommended Starting Dose (MRSD) for "first-in-human" clinical trials

- MRSD frequently based on "no observed adverse effect levels" (NOAEL) in the tested animal species, and conversion of NOAELs to a human equivalent dose with the application of a safety factor
- Assessment of risk/potential benefit for "safe starting dose" using NOAEL may not be equivalent to MRSD dose associated with greatest efficacy in animal studies

54

Third Hypothetical Case Description:

Clinical Trials of Human Neurostem Cells for Neonatal Hypoxic-Ischemic Injury

The following case description uses published information to construct a generic description of a typical clinical investigation that is not unique or specific to any particular product.

55

Background

- Hypoxic-ischemic injury is a common cause of neonatal brain injury in preterm and term infants, leading to significant neurological deficits such as learning disabilities, cerebral palsy or mental retardation.
- Injury to oligodendrocyte precursor cells may contribute to the pathogenesis of hypoxic-ischemic injury by disrupting the maturation of myelin-forming oligodendrocytes.

56

Pre-Clinical Experience

- As documented in the literature, human neurostem cells (HNSC) have demonstrated the capacity to engraft, proliferate, migrate and differentiate into different neural phenotypes in vitro and in vivo, using neonatal mouse models.

57

Study Hypothesis

- These (and other) observations have led to the hypothesis that inserted HNSCs may reduce or reverse the neurological deficit secondary to neonatal brain injury after a hypoxic-ischemic event.

58

Potential Animal Models

- There are several experimental animal models of neonatal hypoxic-ischemic injury that are discussed in the literature.
- Perinatal rodent models have been developed as an experimental platform of hypoxic-ischemic injury for preclinical testing of potential therapeutic interventions. However, they do not reproduce the many distinct physiologic features unique to the premature human infant.
- Other models are thus being developed such as the preterm fetal sheep and non-human primate models (e.g., the preterm baboon and rhesus monkey).

59

Exploring Future Pediatric Clinical Trials

- Several investigators are currently exploring the role of HNSCs in reducing or reversing hypoxic-ischemic injury in these different models in anticipation of pediatric clinical trials.
- Of necessity, the HNSCs would need to be surgically inserted while a child was under general anesthesia – rendering the experimental intervention greater than minimal risk regardless of the risks of stem cell insertion. In addition, the child may need immunosuppressive medication to assure engraftment.

60

Question One

- Please discuss the ethical issues in selecting an appropriate subject population for the initial clinical development plan of these HNSC products.
- Issues you may want to consider include:
  a) differences in the natural history of the disease between adults and pediatric subjects which may influence the timing of HNSC insertion;
  b) whether dosing, safety and/or efficacy should first be established in suitable adult subjects prior to enrolling children; and
  c) differences between pediatric and adult subjects with hypoxic-ischemic brain injury (e.g., possibility of direct benefit, usefulness of safety information, assessment of physiologic response, long-term effects).

61

Question Two

- Please discuss the ethical issues in designing a "first-in-children" clinical trial of these HNSC products.
- Issues you may want to consider include:
  a) the need to establish a sufficient prospect of direct benefit to justify the risk of the experimental intervention;
  b) the range of animal models available for pre-clinical studies;
  c) the different types of physiologic changes in response to the experimental product (e.g., structural, functional, disease reversal);
  d) the severity of the disease; and
  e) the availability of alternative treatments.

62

Committee Discussion

- The Subcommittee discussed the purpose of the study and targeted outcomes -- e.g., the ability to measure physiologic and clinical outcomes -- as important ethical considerations, when designing a study and determining the appropriate subject population.
- The definition and assessment of direct benefit was discussed, including the use of surrogate markers, the pros and cons of younger vs. older subjects, various regulatory approaches for the appropriate review of a pediatric clinical investigation, the use of "compassionate use" and "innovative therapy" models as justifications, limits of animal studies, and the use of adult models as proof of concept prior to pediatric studies.

63

Summary of PES Meeting

- The PES had a rich discussion of the application of 21 CFR 50.52 (greater than minimal risk but presenting the prospect of direct benefit) to FDA-regulated research, using three hypothetical case examples:
  - HIV vaccines in adolescents
  - Inhaled corticosteroids in children with asthma
  - Stem cells for treating neonatal hypoxic-ischemic injury
- The discussion will inform future FDA guidance on the application of 21 CFR 50, Subpart D, to FDA-regulated clinical investigations involving children.

64