COMPLEX ISSUES IN DEVELOPING DRUG AND BIOLOGICAL PRODUCTS FOR RARE DISEASES

JANUARY 7, 2014

SESSION 6: NETWORKS AND COLLABORATIONS IN SUPPORT OF PEDIATRIC CLINICAL TRIALS
CHAIR: ANNE ZAJICEK

- Elements (good and bad) of clinical trials network for pediatric drug/device approval
- Examples of model networks
- Legislation in EU mandates establishing peds networks: effect on pediatric networks in the US
- What does it take to get a peds trial up and running
    - Management infrastructure
    - Protocol with achievable endpoints
    - Clinical investigators capable of enrolling, performing clinical trial
    - Clinical trial materials
    - Patients
    - Data Monitoring Committee
- Role of advocacy groups
    - Encouraging research, development of new therapeutics
    - Definition of meaningful clinical benefit
    - Patient availability
- How to accelerate pivotal clinical trials of new drugs, e.g., through the use of response biomarkers and other surrogate endpoints

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SESSION 7: TOLERATING RISK AND UNCERTAINTY IN PEDIATRIC CLINICAL TRIALS
CHAIR: ROBERT (SKIP) NELSON

An important judgment when developing products for the treatment of rare pediatric diseases is whether there are sufficient data to support giving an experimental drug or biological product to a child. This judgment becomes more critical in the setting of "first-in-human" testing of a product for rare and life-threatening diseases with no known effective treatments that may occur only in children. Panel 7 will focus on three concepts that inform this judgment; the desired clinical benefit, the probability and nature of the harms (i.e., risks) that may be acceptable to attain those benefits, and the amount of uncertainty about these potential benefits and risks that is tolerable.

The data that are needed to support investigational use of a product in children must establish the possibility that each child may benefit clinically from receiving the product. While studies in adults are often used for this purpose, adult data may be unobtainable or uninformative if the disease occurs only in children. As a result, we must use nonclinical (i.e., animal) disease models. However, animal models of a disease may also be unavailable or poorly informative about the human condition. In addition, animal toxicology data may be of limited value depending upon whether normal animals or animals with a disease are used. Finally, it may be scientifically uninformative and/or unethical to ask healthy human adults to volunteer for early phase studies from which we might obtain a maximum tolerated dose and/or preliminary safety data. So we may know little about the potential benefits and risks of an experimental product before the first child is enrolled.

When we consider whether the risks of an experimental product are either "reasonable" or "justified," we should consider both the type of harm that the product might cause, and how likely it is that the harm might occur. What types of harm are we willing to risk given the severity and progression of a child's disease? What amount of uncertainty are we willing to tolerate about the probability of that harm occurring? Given this uncertainty, how do we evaluate whether the animal data are sufficient to proceed with a "first in human" study that administers an experimental product to a child?

Our understanding of the concepts of potential benefit, risks, and tolerable uncertainty may impact on how we apply FDA regulations. For example, FDA regulations at 21 CFR 50.52 provide general criteria for when a pediatric clinical trial may be initiated. Specifically, these regulations require that the prospect of direct benefit from the product be sufficient to justify the risks, and that the balance of risk and potential benefit be comparable to any available alternatives. Similarly, the regulations that must be satisfied when considering expanded access to an investigational drug for treatment use (21 CFR 312.305) require that the potential benefits must justify the risks, and these risks must not be unreasonable given the disease. The expanded access regulations stipulate two additional criteria: (1) the child must be suffering from a serious and/or immediately life-threatening disease for which there are no alternative treatments; and (2)

the expanded access must not interfere with development of the product for eventual marketing approval. This means, for example, that expanded access would not be allowed if too few patients would remain who are eligible to enroll in a clinical trial designed to demonstrate the product's effectiveness.

Each stakeholder in the development of new therapies for pediatric rare diseases brings an important perspective to the judgment that there are sufficient data to support giving an experimental product to a child. An investigator and/or sponsor must review the data and decide whether to initiate a clinical trial. A regulator must decide whether the data are sufficient to allow a clinical trial to proceed. A parent must decide whether to enroll his or her child in a clinical trial. The first half of the session will be a discussion of this judgment among our panel members who represent these various perspectives. We will then turn to the audience to broaden the discussion of this important topic with additional points of view.

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SESSION 8: PEDIATRIC ONCOLOGY
CHAIR: GREGORY REAMAN

Drug approval decisions are predicated on a favorable benefit: risk analysis. In the setting of life –threatening diseases, cancer in particular, the acceptable level of risk of toxicity from a new therapeutic product is likely to be considerably greater than that for many other new drug products. Consideration of benefit and clinically meaningful benefit (impact on a patient's survival, functional capacity, and sense of well being) in the context of limited life expectancy in the advanced stage or relapsed/refractory adult cancer population differs greatly from the perspective which drives new drug development initiatives in children with cancer: optimizing chances for cure and reducing risk of acute and delayed treatment-related toxicities. However, most new cancer drug development in the pediatric population begins in patients in whom the likelihood of cure is unlikely.

- What considerations can and should be given to the clinical benefit which may result from prolonging survival without expectation of cure?
- What other considerations (functional status, quality of life, symptom improvement) are important and how and by whom are they best assessed?
- What level of individual patient safety risk can be tolerated and how/ by whom should this assessment be made?
- Is there a need to expand opportunities for cancer drug development and approval for pediatric indications in second and third line settings as in adult cancers?
- What levels of safety/toxicity risk can/should be considered?

The Pediatric Research Equity Act mandates the evaluation of new drugs and biologics in the pediatric population when the same condition for which approval of a new product is sought exists in children. Although most pediatric cancer drug development leverages adult discovery and development, waivers to study new products are generally sought and approved since most common adult cancers rarely or never occur in children. Nonetheless, some products are and many others may be potentially therapeutically relevant to childhood cancer due to the expressed antigen or genetic lesion targeted by a new drug/biologic or a specific molecular pathway inhibited.

- Given the increasing experience with targeted drug development for genotype-enriched, small sub-populations of adult patients with common malignancies, how best can potential opportunities be exploited to expedite pediatric evaluation of a promising drug/biologic product when indicated?
- What level of non-clinical evidence is required to provide a sound biologic and ethical rationale for early evaluation of potentially relevant targeted drugs in children?
- What extent of adult experience with a new investigational product is required

prior to beginning evaluation in children?

- In the decidedly rare setting of an agent under development specifically for a pediatric cancer indication, how and when should clinical trials begin in children without prior adult testing?

The widely accepted and preferred endpoint for pivotal trials of new drug and biologic products is OS or a surrogate endpoint which is likely to predict an overall survival benefit. The timelines required for front-line pediatric cancer clinical trials which seek to improve long term and disease free survival or likelihood of cure frequently exceed 5-7 years. Consideration of intermediate endpoints or surrogates may facilitate drug development timelines for promising new drugs for childhood cancers.

- What specific intermediate endpoints and response biomarkers could be considered in pediatric clinical trials which are designed to evaluate the benefit of a new product?
- How important are other (beyond improved survival) endpoint considerations in the trajectory of the pediatric cancer experience to new drug development plans for pediatric cancer?
- Is the current pediatric cancer drug development paradigm sufficiently responsive to how children with a cancer diagnosis "function and feel"? Is there a need to address this in the setting of anti-cancer agents, as opposed to supportive care drug development in pediatrics?
- What level of consideration should be given to any specific response outcomes, other than survival or progression of disease when evaluating new drugs for children with cancer?
- Are sufficient objective assessment methods available for use and what level of support should be provided for their development/expansion?

Pediatric cancer drug development is associated with risk. The perspective of risk is stakeholder (patients/parents, investigators, sponsors, regulators) dependent and the context in which these varying perspectives are considered can be a source of considerable confusion. Safety concerns are largely related to risk of acute, persistent, or late toxicity of investigational new drugs particularly in children recognizing their developmental status and increased susceptibility. The risk of the potential for erosion of very good to excellent outcome results of current therapy approaches due to the addition/substitution of an investigational agent in the experimental arm of a clinical trial is a concern to investigators and regulatory agencies. The risk to an individual patient or to populations of children with cancer may be different. The risk of jeopardizing an important drug development plan due to the unanticipated adverse experience in a child is reported to be of concern to sponsors.

- How best can/should safety concerns be adequately addressed to include both individual patient risk and population risk?
- What metric(s) are appropriate for evaluating current outcome results for groups (sub-groups) of patients when considering the evaluation of new drugs/biologics as part of an experimental therapeutic intervention?
- By whom are such metrics derived and evaluated when considering experimental therapies?
- What specific experiences provide the background for the fears of jeopardizing

drug development plans due to unexpected catastrophic event(s) in children?

- How real are these concerns to industry especially given the tightly regulated and clinically protected environments in which trials of investigational agents are conducted?
- How can patient safety risks be clearly separated from business development risks when seeking industry acceptance of plans for evaluation of a new drug product?

New cancer drug development is a global enterprise. International regulatory agencies assume responsibility for the evaluation and approval decisions leading to marketing authorization and distribution of new drugs for the treatment of cancer within their borders with consequences throughout the world. The pediatric-focused legislation which provides regulatory authority to these agencies differs with respect to timelines for submission and extent of proposed pediatric development plans resulting in distinctly different regulatory processes and procedures. These procedural differences are reported to be a source of delay in initiating the early evaluation of new cancer drug products in children.

- What mechanisms exist to foster communication between investigators and regulatory agencies in the U.S. and Europe and how can they be improved?
- What opportunities exist to support a coordinated strategy for the evaluation of a specific investigational agent or class of agents in a given pediatric cancer which would result in an effective collaboration supported by sponsors and regulatory agencies?
- Monthly Pediatric Cluster teleconferences between the EMA and FDA are coordinated by the FDA's Office of Pediatric Therapeutics. What opportunities exist to foster investigator/patient/advocacy group information exchange which would enable more effective and productive bilateral discussions and decision-making?
- How might early transparency in the Pediatric Investigation Plan and Pediatric Study Plan/ Written request processes expedite evaluation and facilitate development when appropriate of promising new drugs and biologics?

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SESSION 9: GENE THERAPY TRIALS IN PEDIATRIC PATIENTS
CHAIR: ILAN IRONY

1. *Development of interventions with long-acting / permanent effects*

Gene therapy may provide the prospect of a cure or substantial amelioration of a condition, after a single administration of the product. Patients may also incur gene-therapy related harms, which may be prolonged or which may appear only after a long interval following treatment. Such harms, for certain viral vectors, may include the risk of insertional mutagenesis and cancer. Please discuss the following issues related to prolonged effects of gene therapy products.

a. **Please** discuss how the requirement for long-term safety follow-up affects the patient's and family's decision to enroll and participate in a clinical trial. Please discuss how sponsors and investigators may assess the balance between long-term benefits and long-term risks when deciding to initiate a clinical trial, and how patients and their families may assess these benefits and risks when deciding to participate in a clinical trial.

b. **Patients** who are being treated with an investigational product often are not eligible to participate in studies of other investigational products. For patients who received a gene therapy, the investigational product may have beneficial or adverse effects for a prolonged period, even the rest of their lives. Therefore, they might be excluded from participation in any studies of newer, perhaps more promising, products for their disease or condition. Please comment, from the sponsor's and investigator's perspective, on the effect that a prior gene therapy may have on the patient's eligibility for subsequent clinical trials. Please comment, from the patient's perspective, on the decision to participate in a gene therapy trial that might preclude enrollment in any subsequent trials of other products.

c. A marketing application can be submitted to regulatory agencies when there is sufficient information to determine a favorable benefit-risk profile for a given disease. Considering the potential for delayed adverse events, please comment on the type and quantity of safety information that would be necessary prior to marketing a gene therapy product, and the type and quantity of safety information that could be deferred to postmarketing studies.

2. *Development of products by individual researchers / academicians, patient advocacy groups or small pharmaceutical companies, rather than large companies*

There are few financial incentives for large pharmaceutical companies to take the risk

of developing therapies for rare diseases. Gene therapies, in particular, present a greater problem because of the time lag in the ability to assess benefits and risks.

a. **Please** describe the challenges and your experiences with regard to obtaining funding for long-term clinical trials.

b. Some sponsor-investigators might not have enough patients with a particular disorder to conduct a clinical trial. Please discuss approaches to foster cooperation, resource- and patient-sharing, and prioritization of products to be tested.

c. A well-established natural history database can be particularly important in the development of gene therapies for rare diseases. Such natural history data can guide the selection of study endpoints (e.g., by determining which outcomes are meaningful to the disease population), can help determine study duration by providing information on the time course of clinical manifestations, and can help determine eligibility criteria and sample size by providing information on the variability of the clinical manifestations. Please describe the challenges and your experiences in the development and conduct of natural history studies to guide clinical development.

3. *Immunogenicity and immune suppression*

When a gene therapy is administered to a patient, the objective is often to express a therapeutic protein. However, such protein expression can elicit an immune response that could interfere with the protein's activity, thereby decreasing any benefit. Such protein expression could also lead to allergic reactions or other toxic effects. Patients may also have pre-existing immunity against viral vectors used as carriers of genes, or may develop new antibodies against these viral vectors after the investigational treatment, particularly if multiple administrations of the product are needed to provide long-term benefit. Suppression of the immune response might be useful to maintain any benefit and decrease some of the risks of a gene therapy. However, immune suppressants have their own toxicities.

a. **Please** discuss whether patients with pre-existing immunity against a vector, or who develop immunity in the course of chronic treatment, can maintain a favorable benefit-risk profile. Please discuss whether patients with pre-existing immunity against the vector, or related vectors, should be enrolled into, or excluded from, early-phase trials. Are the considerations different for late-phase trials?

b. **When** and how should experimental immune suppression regimens be incorporated into studies of gene therapies?

4. *Objectives of early-phase trials (e.g., feasibility in manufacturing, investigator training, goals of dose escalation)*

For small-molecule drugs, dose and dosing regimen exploration is often based on the magnitude and duration of the effect. In addition, for many small-molecule drug or protein products, the clinical benefits and adverse effects appear and disappear relatively quickly, due to the pharmacokinetic properties of these products. This feature of small-molecule drugs makes it sometimes possible to have the same patients participate in more than one clinical trial during drug development, which can be particularly valuable in rare diseases.

a. **In contrast** to small-molecule drugs or proteins, dose and dosing regimen exploration can be challenging for gene therapies, since the duration and control of gene expression are unknown. Please discuss strategies and parameters to be used to find the optimal dose(s) and regimen(s) of a gene therapy product.

b. **In contrast** to small-molecule drugs or proteins, please comment on how the prolonged effects of gene therapies affect the ability of patients with rare diseases to participate repeatedly in multiple sequential studies of gene therapy products, from Phase 1 to Phase 3 clinical development. Please comment on any alternative ways to more efficiently utilize information from patients treated with investigational gene therapies to facilitate the development of gene therapies for rare diseases, such as follow-up of the same patients from early phases of development through Phase 3 for efficacy endpoints or the effects of repeat product administration.

c. **The complexity** of manufacturing gene therapy products often results in limited quantities of products available for a clinical trial. Please describe the challenges and your experiences with regard to manufacturing sufficient amounts of a gene therapy product for efficient clinical development.

5. *Development considerations for invasive procedures that may be used to deliver gene therapies (e.g., to heart or brain)*

Some experimental gene therapies are given intravenously or applied topically to the skin. Others are given through invasive devices and procedures to reach targets deep within the human body, such as the brain, heart or liver. The risks of these more invasive devices and procedures are likely to be higher than the risks of intravenous or topical administration.

a. **From** a sponsor or investigator's perspective, please discuss the safety information about the device or administration procedure that you believe would be necessary before such devices or procedures should be used in gene therapy trials. From a patient's perspective, please comment on how knowledge about the risks of the device or procedure would factor into the overall benefit-risk assessment.

b. **For novel** invasive delivery devices, investigator training may be essential to maintain safety and a therapeutic effect. Please comment on the need and challenges of investigator training to ensure safe delivery of the product. If the training involved is specialized or extensive, please comment on the necessity

and methods for such training of health care providers to ensure the product's safety and efficacy in the postmarketing setting.

6. *Product modifications during development to improve safety*

Gene therapy products are often modified during the pre-clinical and clinical phases of development. These modifications are often intended to improve expression of the gene and the overall therapeutic benefit. As an example, a change in viral vectors might reduce the risk of insertional mutagenesis and cancer. But depending on the specific modifications, there are limitations on the extent to which information regarding one version of a product can be extrapolated to the next version of the product. Thus, well-intended product modifications can translate into delays in the timeline of product development and approval.

a. **Please** comment on the extent that experience with a previous, integrating vector may apply to the new vector. For example, if the transgene remains the same, comment on the situations when new animal studies to support a clinical study of the new vector-gene combination are needed.

b. **Please** discuss the balance between the goal of optimizing the product during development and the resultant delays in bringing the product to market. Please discuss methods to minimize and manage uncertainty regarding the safety of a new version of a product, relative to the previous version, without unduly delaying development.