Applying Regulatory Science to Neonates: Launch of the International Neonatal Consortium

The ABCs of Regulatory Science

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International Neonatal Consortium

Session 1
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Disclaimer

• The views presented here are personal and do not necessarily reflect the views of the Agency
• All specific drug development questions should be discussed with the relevant review division
• Off-label use of drugs will be discussed
Agenda

• US Drug Regulation and Definitions
  - General Considerations
  - Expedited Programs for Serious Conditions
  - Master Protocols
  - Drug Development Tools
    - Biomarkers
    - Clinical Outcome Assessments
  - FDA Drug Development Tool Qualification Program
  - Regulatory Science

• Neonatal Issues
  - Innovative Trials in Rare Diseases
  - Neonatal Specific Diseases
  - Data Standards
  - Consortia Approaches
US Drug Regulation and Definitions
Research and Development Process

SOURCE: PhRMA 2008, Stages of Drug Development Process and attrition rate of compounds as they travel through the drug development process over time.
## Expedited Programs for Serious Conditions (Features)

<table>
<thead>
<tr>
<th>Fast Track</th>
<th>Breakthrough Therapy</th>
<th>Accelerated Approval</th>
<th>Priority Review</th>
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</table>
| • Actions to expedite development and review  
• Rolling review | • Intensive guidance on efficient drug development  
• Organizational commitment  
• Rolling review  
• Other actions to expedite review | • Approval based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit | • Shorten clock for review of marketing application (6 months compared with the 10-month standard review) |

Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics.  
## Expedited Programs for Serious Conditions (Qualifying Criteria)

<table>
<thead>
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<tr>
<td>• A drug that is intended to treat a serious condition <strong>AND</strong> nonclinical or clinical data demonstrate the potential to address unmet medical need <strong>OR</strong></td>
<td>• A drug that is intended to treat a serious condition <strong>AND</strong> preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</td>
<td>• A drug that treats a serious condition <strong>AND</strong> generally provides meaningful advantage over available therapies <strong>AND</strong> demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity of mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)</td>
<td>• An application (original or efficacy supplement) for a drug that treats a serious condition <strong>AND</strong> if approved, would provide a significant improvement in safety or effectiveness <strong>OR</strong></td>
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<tr>
<td>• A drug that has been designated as a qualified infectious disease product</td>
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<td>• Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A <strong>OR</strong></td>
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<td>• Any application or supplement for a drug submitted with a priority review voucher</td>
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Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics.  
Master Protocols

Lung-MAP – the Lung Cancer Master Protocol
A groundbreaking clinical trial model that uses a multi-drug, targeted screening approach to match patients with promising new treatments based on their unique tumor profiles.

http://www.focr.org/lung-map

May include:

- One protocol
- Central governance structure
- Central Institutional Review Board
- Central Data Monitoring Committee
- Central independent review committee
- Central repository of data and specimens
- Leverage common control groups
- Potential to study multiple drugs or multiple markers
Biomarker Definitions

• **Prognostic biomarker**
  - Indicates future clinical course of the patient with respect to some specified clinical outcome

• **Predictive biomarker**
  - Measured prior to an intervention
  - Identifies patients who are relatively susceptible to a particular drug effect versus less susceptible patients

• **Pharmacodynamic biomarker**
  - Response-indicator biomarker
  - Post treatment measurement
  - Marker that reveals whether, or how large, a particular biological response has occurred in that particular patient

• **Efficacy-response biomarker**
  - Efficacy-surrogate biomarker, Surrogate endpoint
  - Subset of general pharmacodynamic biomarkers
  - Predicts a *specific* clinical outcome of the patient at some later time after treatment
Discover a biomarker involved in the mechanism of action of a disease

Test the biomarker in animal models of the disease for use as a diagnostic, predictive, prognostic, or pharmacodynamic biomarker

Test the biomarker in humans with the disease for use as a diagnostic, predictive, prognostic, or pharmacodynamic biomarker
Regulatory Biomarker

“The best setting in which to evaluate a predictive biomarker for an experimental targeted therapy is a randomized clinical trial (RCT) of the targeted therapy vs a standard treatment, where the biomarker status is obtained on the patients but not used to direct treatment.”


“This roles will often involve a quantitative imaging biomarker (QIB), a quantifiable feature extracted from a medical image that is relevant to the underlying anatomical or biochemical aspects of interest. The ultimate test of the readiness of a QIB for use in the clinic is not only its biological or clinical validity, namely its association with a biological or clinical endpoint of interest, but also its clinical utility, in other words, that the QIB informs patient care in a way that benefits patients. But first, the imaging procedure to acquire the QIB must be shown to have acceptable technical performance; specifically, the QIB it produces must be shown to be accurate and reliable measurements of the underlying quantity of interest.”

<table>
<thead>
<tr>
<th>Domain</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Specimen issues</td>
<td>1. Establish methods for specimen collection and processing and appropriate storage conditions to ensure the suitability of specimens for use with the omics test.</td>
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<td></td>
<td>2. Establish criteria for screening out inadequate or poor-quality specimens or analytes isolated from those specimens before performing assays.</td>
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<td>3. Specify the minimum amount of specimen required.</td>
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<td>4. Determine the feasibility of obtaining specimens that will yield the quantity and quality of isolated cells or analytes needed for successful assay performance in clinical settings.</td>
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<td>5. Review all available information about the standard operating procedures (SOPs) used by the laboratories that performed the omics assays in the development studies, including information on technical proficiency, reagents, analytical platform, assay scoring, and reporting methods, to evaluate the comparability of the current assay to earlier versions and to establish the point at which all aspects of the omics test were definitively locked down for final validation.</td>
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<td>6. Establish a detailed SOP to conduct the assay, including technical protocol, instrumentation, reagents, scoring, and reporting methods, calibration, and analytical standards, and controls.</td>
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<td>7. Establish acceptability criteria for the quality of assay batches and for results from individual specimens.</td>
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<td>8. Validate assay performance using established analytical metrics such as accuracy, precision, coefficient of variation, sensitivity, specificity, linear range, limit of detection, and limit of quantification, as applicable.</td>
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<td>9. Establish acceptable reproducibility among technicians and participating laboratories and develop a quality assurance plan to ensure adherence to a detailed SOP and maintain reproducibility of test results during the clinical trial.</td>
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<tr>
<td>Model development, specification, and preliminary performance evaluation</td>
<td>10. Establish a turnaround time for test results that is within acceptable limits for use in real-time clinical settings.</td>
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<td>11. Establish whether any additional steps, cutoffs, or points on the assay are affected by sample characteristics that are not handled uniformly or systematically.</td>
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<td>12. Establish a method to detect and report any deviations from expected performance.</td>
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<td>13. Establish whether all clinical validations of the predictor were analytically rigorous and unequivocally defined.</td>
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<td>14. Establish whether the predictor algorithm, including all data preprocessing steps, cutoffs, and quality control measures, was validated.</td>
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<td>15. Establish whether the predictor algorithm was validated in a prospective, retrospective, or both, manner.</td>
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<td>16. Establish whether the clinical utility of the omics test was evaluated by using stored specimens from a completed clinical trial (that is, a prospective, retrospective study).</td>
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</table>

**Criteria for the use of omics-based predictors in clinical trials**

Examples of the Criteria for the Use of Omics-Based Predictors in NCI Supported Trials

• Specimen issues
  – Determine the feasibility of obtaining specimens that will yield the quantity and quality of isolated cells or analytes needed for successful assay performance in clinical settings

• Assay issues
  – Validate assay performance by using established analytical metrics such as accuracy, precision, coefficient of variation, sensitivity, specificity, linear range, limit of detection, and limit of quantification, as applicable

Examples of the Criteria for the Use of Omics-Based Predictors in NCI Supported Trials

• Model development, specification, and preliminary performance evaluation
  – Evaluate data used in developing and validating the predictor model to check for accuracy, completeness, and outliers. Perform retrospective verification of the data quality if necessary

• Clinical trial design
  – Provide a clear statement of the target population and intended clinical use of the predictor and ensure that the expected clinical benefit is sufficiently large to support its clinical utility

• Ethical, legal and regulatory issues
  – Establish communication with the individuals, offices, and agencies that will oversee the ethical, legal, and regulatory issues that are relevant to the conduct of the trial

Support for Use of Surrogate Biomarkers

<table>
<thead>
<tr>
<th>Fact (surrogate)</th>
<th>Supports Surrogate</th>
<th>Does Not Favor Surrogate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological plausibility</td>
<td>Epidemiologic evidence extensive and consistent</td>
<td>Inconsistent epidemiology</td>
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<tr>
<td></td>
<td>Quantitative epidemiologic relationship</td>
<td>No quantitative epidemiologic relationship</td>
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<tr>
<td></td>
<td>Credible animal model shows drug response</td>
<td>No animal model</td>
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<tr>
<td></td>
<td>Well-understood disease pathogenesis</td>
<td>Pathogenesis not clear</td>
</tr>
<tr>
<td></td>
<td>Drug mechanism of action well understood</td>
<td>Novel actions not previously studied</td>
</tr>
<tr>
<td></td>
<td>Surrogate relatively late on biological path</td>
<td>Surrogate remote from clinical outcome</td>
</tr>
<tr>
<td>Success in clinical trials</td>
<td>Effect on surrogate has predicted outcome with other drugs of same pharmacologic class (supports surrogate in class)</td>
<td>A negative outcome without clear explanation</td>
</tr>
<tr>
<td></td>
<td>Effect on surrogate has predicted outcome in several classes (supports more general use)</td>
<td>Inconsistent results across classes</td>
</tr>
<tr>
<td>Risk-benefit, public health considerations</td>
<td>Serious or life-threatening illness and no alternative therapy</td>
<td>Nonserious disease and alternative therapy with different pharmacologic action known to affect outcome</td>
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<td></td>
<td>Large safety database</td>
<td>Little safety data</td>
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<td>Short-term use</td>
<td>Long-term use</td>
</tr>
<tr>
<td></td>
<td>Difficulty of studying clinical end point (rare, delayed)</td>
<td>Easy to study clinical end point (short-term study)</td>
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<tr>
<td></td>
<td></td>
<td>Long-delayed, small effect in healthy people</td>
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</tbody>
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Surrogate Endpoint Challenges

Clinical Outcome Assessments

• Clinical outcome assessments (COAs) measure a patient’s symptoms, overall mental state, or the effects of a disease or condition on how the patient functions. COAs can be used to determine whether or not a drug has been demonstrated to provide treatment benefit. Treatment benefit can also be defined in terms of a safety benefit compared to other treatments. A conclusion of treatment benefit is described in labeling in terms of the concept of interest, the thing measured by the COA.

• Four types of COAs
  - Patient reported outcome (PRO) measures
  - Clinician reported outcome (ClinRO) measures
  - Observer reported outcome (ObsRO) measures
  - Performance outcome (PerfO) measures
Drug Development Tools Qualification

- Clinical Outcome Assessments
- Biomarkers
- Animal Models (Animal Rule)
- DDT Qualification
Drug Development Tools Qualification

• Concept: Qualification is a conclusion that within the stated context of use, the results of biomarker measurements can be relied upon to have a stated interpretation and utility
  – Context of use to be clearly specified

• Regulatory implication: Can rely upon using the biomarker in the qualified manner in the IND period, and in NDA and BLA submissions, without needing to resubmit extensive data and request that the relevant CDER review group consider and reconfirm the biomarker

• Importance of predictive and prognostic biomarkers, not just biomarkers as surrogate endpoints
Biomarkers in Drug Development

**Objective:** Use the biomarker in a single drug development program

- **Acceptance through IND, NDA and BLA submissions (Drug approval process)**

- **Responsible Parties:** One sponsor contacts the review division
- **Process:** Discuss, provide rationale and data to the review division
- **Risk and resource:** burden on one sponsor
- **Biomarker Information:** Embedded in drug labels

**Objective:** Establish the biomarker for use in multiple development programs

- **Biomarker Qualification**

- **Responsible Parties:** Generally, consortia contact the BQ Program
- **Process:** Submit letter of intent. Follow the BQ process
- **Risk and resources:** shared among consortia members
- **Biomarker Information:** qualified biomarkers announced as draft guidance
Opportunities for Biomarker Development

- **CPIM**
  - Exploratory Discussions

- **Letter of Support**
  - Pre-Qualification
  - Time: 2 – 3 months

- **Qualification – Limited Context of Use**
  - Initiation
  - Consultation & Advice
  - Review
  - Time: 3 – 4 months

- **Qualification – Expanded Context of Use**
  - Initiation
  - Consultation & Advice
  - Review
  - Time: 1 – 2 years

- **Time**
  - 2 – 3 months
  - 3 – 4 months
  - 1 – 2 years
  - 2 – 3 years
Reproducibility of Published Data

Relationship of published data to in-house data (Bayer HealthCare) for drug targets

Prinz F, Schlange T, and Asadullah K. 2011. Believe it or not: how much can we rely on published data on potential drug targets? Nature Reviews Drug Discovery. 10:712-713.
Regulatory Science

Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

<table>
<thead>
<tr>
<th>Table 1: Seven CDER Drug Safety-Related Research Needs</th>
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<tbody>
<tr>
<td>1. Improve access to postmarket data sources and explore the feasibility of their use in safety signal analyses</td>
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<tr>
<td>2. Improve risk assessment and management strategies to reinforce the safe use of drugs</td>
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<tr>
<td>3. Evaluate the effectiveness of risk communications of drug safety information to health care providers and the public</td>
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<tr>
<td>4. Improve product quality and design, manufacturing processes, and product performance relating to safety</td>
</tr>
<tr>
<td>5. Develop and improve predictive models of safety in humans, including nonclinical biomarkers</td>
</tr>
<tr>
<td>6. Improve clinical trial statistical analyses for safety, including benefit-risk assessment</td>
</tr>
<tr>
<td>7. Investigate clinical biomarkers of safety, including standards for qualification</td>
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Neonatal Issues
Right Drug

Right Population

Right Dose

Right Trial Design

Right Endpoints
Ivacaftor

- Two randomized double-blind placebo controlled clinical trials (n=213) in cystic fibrosis (CF) patients with \(G551D\) mutation in the \(CFTR\) gene
- Third most common CF mutation (worldwide ~3%)
- Primary efficacy endpoint – improvement in lung function as determined by the mean absolute change from baseline in percent predicted pre-dose FEV\(_1\) through 24 weeks of treatment
- No direct correlation between decrease in sweat chloride levels and improvement in FEV\(_1\)

*Primary endpoint was assessed at the 24-week time point.*
Innovative Trials in Rare Diseases

- **Carglumic acid for N-acetylglutamate synthase (NAGS) deficiency**
  - Rare urea cycle disorder (~10 patients in U.S.)
  - Retrospective review of a 23 patient case series in Europe
  - Short-term (ammonia) and long-term (neurocognitive) outcomes
  - Compared to historical control (not formally conducted)

- **Deferiprone for transfusional iron overload in patients with thalassemia syndromes not responding to other therapies**
  - Planned pooled analysis of patients from several studies (n=236)
  - Endpoint was change in serum ferritin, not a clinical outcome

- **Cysteamine bitartrate for nephropathic cystinosis**
  - 2 open-label studies (n=94) children treated with product or innovator cysteamine HCl
  - Largely a pharmacodynamic comparison based on WBC cystine levels vs. historical control pharmacokinetic/pharmacodynamic levels
Drug Development Disconnect

Majority of drugs used are off-label

Very few new therapies are being developed specifically for neonates

28 drugs studied in neonates
- 46% not used in NICUs
- 29% used in fewer than 60 neonates

Neonatal Issues

Patients → Conditions → Treatments → Endpoints

- Neonatal populations
  - Extreme prematurity
  - SGA
- Biomarkers
- Confounding conditions
- Risk of unique adverse events (IVH, NEC, PPHN)
- Ethics
- Role of parents/staff

- Unique conditions
  - PPHN
  - HIE
  - IVH
  - RDS
  - CLD
  - NEC
  - Diseases not able to be extrapolated from adult disease

- Absorption
- Distribution
- Metabolism
- Excretion
- Equipoise
- Formulations

- Efficacy endpoints
  - Definition of normal
  - Differ from adult definitions
  - Short term and long term
  - Discharge criteria
  - Neurodevelopmental outcomes

- Safety endpoints
  - Short term and long term
Data Standards

Massive amounts of clinical research data in extremely disparate formats

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Development of Consortia

1. Identify Need/Public Health Question
2. Leverage resources/expertise
3. Identify partners and define roles and responsibilities
4. Develop proposals, timelines, milestones, deliverables
5. Share data in the public domain
Basic Science Research
- Natural History
- Pathophysiology of Disease
- Ontogeny of Metabolic Pathways
- Micro-assays

Clinical Trials
- Innovative Designs
- Biomarkers
- Clinical Outcome Assessment Tools
- Network Sites

Definition of Endpoints
- Clinically Meaningful
- Short Term/Long Term

Consortia
- Leverage Insights
  - Academia
  - Government
  - Industry
  - Patient Advocacy Groups

Modeling and Simulation
- Ontogeny of Metabolic Pathways
- PK-PD Studies

IT Delivery Systems
- Interoperable Systems
- Standardized Data
- Standardized Case Report Forms

Impact to Patients
- Better Dosing
- More Appropriate Use of Current Drugs
- Increased Access to New Drugs

Neonatal Drug Labels
How Can the INC Be Impactful?

• Can we articulate clinical pharmacology needs for the neonate?
• For key therapeutic areas
  – Is there a need for animal models?
  – What are the basic science needs to support modeling and simulation?
  – What populations should be studied?
  – What would be clinically meaningful biomarkers for this population?
  – Is it possible to develop registries or databases for this population? What are the data standards and how will this data be curated?
• Are there others who can partner with INC?
Neonatal Clinical Pharmacology White Paper Considerations

• General
• Impact of developmental changes on variability in drug disposition and effects in newborns
• Use of clinical pharmacology data in neonatal drug development
• Timing of initiating clinical trials
• Methodological aspects of neonatal clinical pharmacology study design: What is relevant?
• Data analysis
• Formulations
• Glossary of terms