Pediatric Issues for *in Vitro* Diagnostic Devices (IVD)

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What is an IVD?

- In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation and examination of specimens...

  21 CFR Subpart A §809.3
Pediatrics are left out

- Especially when:
  - New companies
  - New technologies
  - Peds only a small part of population

- Why?
  - Logistics of “getting off the ground”
  - Cost factors
  - Unspoken inevitability of off-label use
Topics

When and why pediatric information is important:

I. Reagents and instruments
II. Systems

III. What is being done to encourage pediatric IVD development
I. Reagents and Instruments

Why is it important?

- Examples of reagents and instruments
  - Test ordered by physician or OTC tests
  - Screening for cancer, pregnancy test, glucose

- Reference ranges (what is normal)
  - Established during clinical studies, $$
  - Affects S & E
Reagents and Instruments
How it impacts S & E

- Ped reference ranges often differ from adults
- Cannot rely on adult ranges
  - Some analytes- subtle differences
    - electrolytes and blood glucose
  - Others- stark differences
    - bone and liver enzymes
    - steroid hormone values
  - New tests or technologies- unknown???
What happens when pediatric reference ranges aren’t provided?

- Labs must develop their own ranges - time & $.
- Difficult to identify enough children
  - who represent “normal” population
  - Include all conditions where range may vary

- Result:
  - Poor study (inaccurate range…if study is done)
  - ↓ n, not stratified by relevant subgroups, not stat powered
  - Study often enrolls sick children or they reflect the local population’s racial and ethnic mix.
What’s the impact of not having ped ranges (or inaccurate ones)?

- No alternatives - discretion of physician
- False sense of security

- Potential to subject other children to:
  - inaccurate diagnoses
  - unnecessary diagnostic procedures
  - inappropriate treatment.
II. In Vitro Diagnostic Systems

What are we talking about?

- “Systems”
  - Complex testing device operated by peds (or parents)
  - Measuring samples from peds

- Example- Continuous Glucose Monitor (CGM)
  - Inserted into abdomen, measures every 5 min
  - Limited intended use- tracking and trending (not dosing)
  - Requires actions (calibrate, change sensor, respond to alarms)

- Pediatric use impacts S & E
In Vitro Diagnostic Systems
Three factors impacting S&E

1. Human Factors (HF)
2. Device design
3. Physiology
HF

- How people interact with the device
  - Behaviorally
  - Physically

- Different skills and abilities

- Compliance, not following directions
  (Teens and pre-teens)
Following instructions

- Size and complexity of manual
- Proper storage (meter test strips)
- Running quality control to verify its working properly
- Short cuts
- Use beyond expiration
- Using according to labeled indications for use not contrary to limitations- “it won’t happen to me”
Physiological Differences

- Activity levels, diet effect CGM performance
- Controller (algorithm) converting raw electrical signal to a glucose value is designed for adults
- Alarms (hypo and hyperglycemia)
  - Not hear them at night
  - Not pay attention to them or turn them off (HF)
Device Design

- Size & physical design
  - Safe for more sedentary adults
  - Sensors break off
  - Dislodged through activity - interrupts signal

- Typically - lack built-in safeguards
Consequences of not having Ped customized test system

- Physicians prescribe adult tests
  - no alternatives
- HCP are forced to make decisions without knowing
  - Whether it affects
  - How
  - To what degree does it affect
- May submit request for ped use & approved
  - May not be optimized for ped use- no alternative
III. What is being done?

$\textbullet$ User Fees

### User Fees for 510(k)s

#### Standard User Fees/Small Business

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Large Business</th>
<th>Small Business</th>
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<tr>
<td>FY 2010</td>
<td>$4,007</td>
<td>$2,004</td>
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<tr>
<td>FY 2011</td>
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<tr>
<td>FY 2012</td>
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User Fee is Waived

- Law requires payment of a user fee unless device qualifies for one of the exceptions.

- …your submission is for a device intended **solely** for a pediatric population.
What is being done?

Funding for research
The National Children’s Study - A Focus on Environment Children’s Health Act of 2000

- Large & comprehensive study- how genes & environment interact to affect children’s health.
- Tracks the health and development of more than 100,000 children from before birth to age 21.
- Led by the National Institute of Child Health and Human Development (NICHD) in collaboration with National Institute of Environmental Health Sciences (NIEHS), CDC, and the U.S. Environmental Protection Agency (EPA).

- NCS will provide information
  - prevention strategies
  - health and safety guidelines
  - possibly new treatments and cures for disease.

http://www.nationalchildrensstudy.gov
Big Study on Small Patients

National Children’s Study Could Provide Key to Standardized Pediatric Reference Intervals

By Deborah Levenson

Reference intervals for infants and children are notoriously difficult to define, oftentimes forcing hospital labs to develop their own intervals with little data. If a proposal from AACC’s Pediatric Reference Range Committee moves forward, the National Children’s Study may be the key to developing standardized intervals for several common analytes.
American Association of Clinical Chemists Proposal

- AACC’s Pediatric Reference Range Committee preparing a proposal
- Conduct research that would establish age-related Reference Ranges
- Adjunct to the NCS
- Access to > 20 years worth of samples from 100,000 children across the nation.
CONCLUSIONS

- Generally Ped info only needed when:
  - Reference ranges are different
  - When physical size & design impacts it’s function (S&E)

- More is being done:
  - User Fee $ & research
  - Awareness
We know where we want to be but not sure of best way to get there...
NCS Details

- To establish links between children’s environments and their health, researchers will analyze how various factors—including chemical, physical, biologic, geographic, and social and behavioral elements—interact with each other and what helpful or harmful effects they might have on children’s health.

- Look for links between these factors and health issues such as birth defects and pregnancy-related problems, injuries, asthma, obesity, diabetes, and behavior, learning, and mental health disorders. By tracking children’s development through infancy, childhood, and early adulthood, researchers hope to pinpoint the root causes of these and many other childhood and adult diseases.

- “Uncover important health information at virtually every phase of life.

- NIH’s Eunice Kennedy Shriver NICHD, one of the consortium of federal agencies implementing the study.

- Provide major insights into disorders of birth and infancy, such as preterm birth and its health consequences. Ultimately it will lead to a greater understanding of adult disorders, many of which are thought to be heavily influenced by early life exposures and events.”

- [http://www.nationalchildrensstudy.gov](http://www.nationalchildrensstudy.gov)