NATIONAL INSTITUTES FOR CHILD HEALTH AND HUMAN DEVELOPMENT

PEDIATRIC PHARMACOLOGY RESEARCH UNIT CAPABILITIES

INTRODUCTION

This report is an assessment of the current capabilities of the Pediatric Pharmacology Research Units (PPRU) of the National Institute for Child Health and Human Development (NICHD) Maternal and Child Health Branch, their strengths and weaknesses as a clinical research network, and their vision and mission for the future in the context of increasing the available of pediatric drugs and formulations. Although data was collected from sources outside the Network Principal Investigators and key staff, the predominant perspective portrayed in this report is from internal sources, not from external sources or customers of the Network.

STUDY METHODOLOGY

In this study information was collected through surveys and interviews and focused on three areas:

- a complete inventory of the PPRU site capabilities,
- the strengths and weaknesses of the PPRU network organization, and
- the 3-5 year projections for PPRU Network operations.

Survey instruments were provided to Principal Investigators and selected key staff for preparation of background information. Survey questions were administered via one-on-one telephone interviews. NICHD, PPRU Network Project staff and FDA were also interviewed.

The capabilities portion of the survey consisted of a list various services, functions and technologies generally provided by contract research organizations (CROs). This list was developed by analyzing promotional and advertising materials and interviewing CRO executives. This list provided a basis comparison between PPRU capabilities and those currently available in the marketplace and will be the basis for future PPRU promotional materials. Disease focus and other capabilities are summarized at Attachment A.

The survey addressed interviewee views of the strengths and weaknesses via standard open-ended questions. Data were gathered via anonymous telephone interviews. Some direct, de-identified quotes and information will be used in this report. Summary statements are the consensus of opinions with actual quotes provided for supportive data and completeness of information.

Many of the “open-ended” questions of the survey centered on the “Mission, Vision, and Values” of the PPRU as seen by its members and the NICHD. The strengths, and weaknesses of the network and the potential growth and opportunities for them was also queried. Some questions sought to elicit more clarity around the business operations aspect of the network.

SURVEY RESULTS

PPRU Capabilities

From the capabilities section of the interviews, it was almost unanimously agreed that every expertise necessary for conducting highly sophisticated pharmacological pediatric trials is present within the PPRU network. Some centers had strengths in particular areas not shared by other centers, but *together*, all seven units had every capability. The most predominant weakness observed and agreed upon by all was the lack of a central data collection and processing function for the units. Most agreed also that they needed to do better at independent quality reviews and producing health economic outcomes data.

The survey also showed that two "tiers" of capabilities exist with-in the units.

- One "tier" is the "core" tier which consists of basic and fundamental capabilities which must be present in order for the units to be a member of the PPRU.

- The second "tier" is the "specialty tier" consisting of capabilities above and beyond the "core" and particular to that unit.

To add further depth to these capabilities: various levels of quality and quantity exist with-in each "tier" , with-in each unit, as well.

Thus, although each unit can stand alone as a research unit, the true strength and power of the product and the clinical trials conducted is derived from the completeness of all the units functioning as a "whole". This underscores the necessity for the PPRU to maintain a very high level of coordination and communication amongst themselves and the NICHD. Network coordination needs to be very well defined and articulated so as to leverage the strengths of each center and to make one strong, unified whole.

Strategy, Mission, Vision, Values, Operations

The Strategy, Mission, Vision, Values section of the surveys also revealed highly consistent answers from the participants. All units are highly aware of the purpose for the formation of the PPRU and are very dedicated to providing top-flight pediatric clinical trials.

However, while all participants could agree to the short-term vision and mission for the PPRU, all expressed significant doubts about the long term goals for the PPRU by the NICHD. All members of the PPRU expressed desires to be a stand-alone unit within five years, however, their wishes were tempered by the funding realities and the administrative and organizational limitations.

STRENGTHS AND WEAKNESSES OF THE PPRU NETWORK

Nearly unanimous was agreement that the greatest strength of the PPRU is the very high level of commitment and dedication from the department Heads, PharmD's and the staff of the units to delivering superior quality pharmacological pediatric studies and their commitment to bettering the health of children and medicines to treat various diseases.

The clinical and scientific skills and expertise found in each unit is signicant. It is clear that no other network exists in the country that could deliver the level of sophistication of pediatric clinical trials than the PPRUs.

Strengths Summarized

- Diverse (socioeconomically, culturally and medically) patient population
  - Very large patient population to draw from for clinical trials
  - Superior knowledge of, and access to children(from infants to teenagers)

- Superior skills in pediatric pharmacology, pharmacokinetics, drug metabolism, dosing, and bioavailability and data collection
  - Top expertise in conducting trials in children
  - Expertise in protocol development and study design which facilitates recruitment, timely completion of studies, cost savings for pediatric trials."
  - More sophisticated studies, scientifically rigorous than CRO's
  - Can provide great clinical research and practical patient management which results sophisticated studies coupled with the realities of patient management
  - The network is on par with existing adult cooperative study groups
  - Excellent record of tracking drug excretion in breast milk.

- Equal or Superior Capabilities than CROs
  - More sophisticated studies, scientifically rigorous than CRO's.
  - Don't have to worry about as much profitability as the CROs; we have more flexibility, less overhead, and can afford to adhere to very rigorous scientific protocols and studies"
  - The biggest advantage the PPRU has over CROs is that primary investigators have done a lot of pediatric trials. CRO's usually only recruit office-based patients, which makes for a very limited patient population and ability to monitor such things as adverse reactions of high quality data.

- Physician representation from all pediatric specialists.
  - While the CRO's would have to go to multiple sites to get the range of physician specialists, each center in the PPRU has them all present in one place.
  - Because the PPRU is made up of clinicians which are skilled in both treat clinical research and practical patient treatments, they can bring a very sophisticated approach to clinical trials coupled with the realities of patient management.

- NIH Affiliation
  - The NICHD gives incredible stature to the PPRU. We must never lose sight of that.
  - The NICHD should not withdraw its support and affiliation with the PPRU. It affords the PPRU prestige and space within the universities with which they are affiliated.
  - The NIH affiliation affords much credibility to, and validation of the PPRU.

- Motivation and dedication of the PPRU
  - The motivation and dedication of the primary investigators of the PPRUs is unparalleled.

WEAKNESSES

The biggest frustration expressed in the survey centered on business and administrative deficiencies. Many business processes and systems are lacking which could drive projects, legal documents, and protocol approvals in a more timely and efficient way. Although all participants admitted that there has been some improvement recently, they felt that the business aspects are not progressing at a rate that will keep pace with the demands for clinical trials. There is concern these weaknesses will hamper the PPRU mission. Nearly all interviewees felt there should be a more centralized organization for providing business operation plans and the execution of them.

Communications between the individual units of the PPRU, and the PPRU and the NICHD was also deemed to be lacking. Although the biweekly teleconferences have substantially improved the communications between the units, they felt the part-time staff assignments of the NICHD often crippled their efforts to extend these communications up through the NIH.

One of the most compelling weaknesses uncovered in this survey is the substantial challenge to the individual units to answer to "many masters;"

- The individual goals of the unit to conduct clinical trials for pediatrics;
- The goals of the PPRU;
- The goals of the NICHD.

In addition to meeting the goals of those three, the units are also required to meet the expectations and objectives of the universities in which they are located.

PPRU units continually juggle all their communications, objective planning, and resource allocations to meet the needs of all four "masters."
To effectively manage, they need specific business and operations plans. Yet, their time and energy are already spread very thin and the thought of having to produce their own documents and plans may jeopardize their ability to focus on the clinical and investigative duties to which they are committed.

Finally, all unit members felt that there is a need for better advertising and promoting the skills and capabilities of the PPRU to the medical community and industry. Without the awareness of the PPRU by their customers, they will never achieve the level of activity and stature they will need to sustain their growth and success.

Weaknesses Summarized

- Insufficient funding
  - Lack of funds to reimburse patients for expenses
  - Not enough 'seed' money to hire sufficient FTEs for recruitment etc., requiring PPRUs borrow recruiters from other sites to help enroll patients because the PPRU does not have enough working capital to deep on adequate staff.
  - No flexibility to expand and contract the number of people to gear up for studies.

- Weak industry relations
  - Industry relations are not consistent across units of the PPRU as a whole
  - The PPRU is not well known by pharmaceutical companies or biotech companies
  - Poor communications to customers about capabilities and expertise of the PPRU.
  - No central phone number, address, 800#, etc. for customers or industry to contact if they want to initiate a trial.

- Limited electronic data technology
  - Data entry technology and processes need improvement.
  - Central archiving of data not consistently available.
  - Lack one site that is responsible for all data collection and processing.
  - Lack of a data coordinating center to compete effectively against the CROs

- NIH affiliation
  - Insufficient clinical trial experience in the leadership of NICHD creates communication and administrative difficulties.
  - PPRU affiliation with the NIH brings prestige, bit also red tape" and regulations

- Inadequate central organization and business processes.
  - No core identity or central coordination of activities
  - No central marketing function

CONCLUSION

The PPRU network has amassed a superior expertise in conducting highly sophisticated pharmacological pediatric studies in the United States. This represents a substantial contribution to the medical community, industry and to the treatment of diseases of children.

Scientific and clinical operations are established. PPRUs now need established business operations, which are much more focused and organized, including business analysis, strategic planning and operational planning.

In order to move the operations of the Network forward in its development towards self-sufficiently from government funds within 3-5 years a number of issues require resolution, as noted in the recommendations.

RECOMMENDATIONS

Clarify near-term deliverables and long-term objectives

It is not clear to the PPRU Network Centers what near-term deliverables are required and how success will be defined. Is success defined as:

- The number of studies initiated or completed in a particular year?
- The number of studies funded by industry?
- The number of Network studies? The number of Center studies?

The RFA is silent on this point and the Principal Investigators are understandably in need of clear communications about what targets they are expected to hit.

It is also unclear what long-term objectives NICHD has established for the Network.

- Does the NICHD intend to fund the Network for the next grant renewal period?
- If so, does it has plans to increase, stabilize or reduce the funding?
- Does it intend that the Network become self-sufficient during the current grant period, or at some later time?

Principal Investigators have dedicated substantial Center and personal resources to assist in the PPRU project and must balance the interests of their Centers and Universities and therefore they need clear information from NICHD. This is particularly true in those areas of the country where health care system changes have influenced the availability of clinical research funding.

Clarify control/autonomy over studies

It is not clear to PPRU Principal Investigators whether they have the autonomy to decide whether or not to participate in studies without retaliation by the NICHD. Centers serve the needs of their own organizations and universities and while some trials may be attractive to the PI, they may be in conflict with the other players in their systems.

Further, the local protocols managed by the Centers can be used to promote the image and expertise of the Network as a whole. Government funding represents a small part of the total funding needs of the Centers and should not be used as a control over substantial decisions. For the Network to succeed over time, the autonomy of every location must be preserved.

Develop inter-Center relations and familiarity

The relations between cooperating centers will develop over time and through repeated contact and collaborative effort. Likewise, the familiarity of each PI with the capabilities of the other Centers is important and requires effort and extensive communications.

Current biweekly telephone calls and quarterly meetings are insufficient at this stage of the Network's development. Additional opportunities to communicate are needed. Strong central management could assist in those communications.

Develop central management and business operations

The complexity of network operations is reaching a breaking point. PPRUs need logistical support, timely review and approval of all protocols and requests for information, as well as high quality marketing and public relations.

The PPRU network is a substantial asset of scientists, studies, capabilities and intellectual property. Its assets can be used to generate income as third-party spokesmen and as experts in pediatric pharmaceutical care.

Working Assumptions Related to PPRU Success

General Assumptions. The dearth of pediatric pharmaceuticals and formulations is the result of numerous scientific, clinical, economic, political and cultural barriers to development. Some of these barriers have been totally or partially removed. Some remain. The scientific, clinical and methodological barriers which PPRUs were intended to resolved cannot overcome the new financial barriers of the current healthcare economic climate. As a result, there are still significant hurdles to clear. The result is less than optimum pharmaceutical care for children.

NICHD Organizational Assumptions. NICHD has an interest in assuring the success of the PPRUs for reasons which go beyond the development of *specific* pharmaceutical products and formulations. PPRU assets represent a core of expertise which can be leveraged in the future to promote the appropriate development and use of pediatric pharmaceuticals beyond the grant funding period. Dispersion of those assets or the erosion of those assets if the PPRU focus is lost would significantly harm future progress in this therapeutic arena.

NICHD has plenty of enthusiasm for this effort, but like the rest of the NIH, it is increasingly threatened by budget-cutting exercises. Only the most productive programs will survive scrutiny and NICHD will not be able to nurture the PPRUs for an indefinite time while it awaits the returns on its investments. It is likely that the NICHD will be able to support the program in several ways, however: first, through additional promotional efforts to assure progress in the area of pediatric pharmaceuticals development and PPRU study placement, second, through in-kind support, third, through modest increases in financial support and fourth, through interventions to secure institutional change within FDA related to pediatric pharmaceuticals beyond the term of the current Commissioner.

FDA Organizational Assumptions. Senior FDA officials have expressed public interest in expediting pediatric pharmaceutical and formulation regulatory review and approvals and FDA has devised organizational solutions to communications in this area. This interest will not outweigh the statutory requirements and cultural dynamics within the agency to protect the public health. As a result, it is likely that companies will perceive FDA actions in the regulatory process as "business as usual."

PPRU Assumptions. PPRU investigators had contacts within companies and are familiar with the requirements of companies for studies. Principal investigators had a record of success in drug development studies. Changes in the industry have introduced new players in companies and in the industry (Contract Research Organizations in particular) which may impede progress and create competition.

PPRU investigators are known as clinical "thought leaders" in their field by companies and among their clinical peers. This expertise, which is helpful in encouraging companies to place studies in research centers, is less beneficial as marketing departments decline to move forward with pediatric indication development and promotion.

PPRUs have the experience and capabilities to produce timely, cost-efficient studies which meet the requirements of companies and PPRU funding and infrastructure are adequate to sustain the clinical development capacity provided that companies can cost- and/or work-share. The emergence of CROs, however, create a level of competition for which "adequate" is no longer sufficient.

Pharmaceutical Industry Assumptions. Pharmaceutical companies were contacted at the time the PPRU program was designed and many were curious (if not interested) in the development of the Units. At least one company had attempted to develop a similar network -- without success. Since that time, financial pressures have created dramatic changes in industry. As a result, companies have reinstated their resistance to pediatric product development investments.

Some companies will be willing to pursue product development if the development and regulatory processes are facilitated.

Some companies are willing to pursue development but are uninformed about the need for pediatric products and the recent facilitation by the NICHD, PPRUs and FDA.

Public Policy Assumptions. There will be no significant events which will change the current lack of focus on children. Political seasons and rhetoric about caring for children will wax and wane, as they have during PPRU development, but this will not result in any changes in funding. Deficit reduction efforts will continue, driving down available resources and increasing the competition for funding. Research will compete unfavorably against medical care for federal funds. Children will compete unfavorably against the elderly for medical care funds.

We have also discussed a number of **pediatric product development issues** as a part of the context of our work.

Policy and Political Issues. National policy interest in specific issues such as this one are usually cyclic, alternately peaking at fairly predictable intervals. Pediatric product development is currently enjoying a peak, with a convergence of professional interest, scientific opportunity and regulatory relief. It is unlikely that this peak will continue for much longer, however. Competition for attention to other issues will emerge and will likely succeed in drawing away

attention. Children's advocates, whose style has historically be confrontational, are unlikely to maintain a productive focus on this area.

FDA Organizational Issues. FDA has substantial interest in pediatric pharmaceuticals. The Commissioner has initiated programs to facilitate product development and FDA is conducting its own review of pediatric drugs. However, the relationship between companies and the FDA is fragile and uncertain. Companies are unlikely to take risks on any product and in particular in a vulnerable population such as children lest they damage their other agendas with FDA. Regardless of the Commissioner's personal interest, the individual reviewers at the agency are accountable for their product approval recommendations and are unlikely to allow the Commissioner's interest to override their statutory and personal responsibilities to protect the public's health.

NICHD Organizational Issues. NICHD's development and interest in the PPRUs is a strength of the organization and creates opportunities to facilitate additional research. However, NICHD has a mixed track record of drug development. It also has cultural conflicts with the FDA and the industry it is courting in this project. Industry and academia have similar cultural conflicts.

Business/Commercial Organizational Issues. Industry opportunities are emerging --some generic drug firms are developing on-patent drugs, biotechnology companies are beginning to grow again and traditional pharmaceutical firms are more interested in research and marketing in niche areas. On the other hand, income pressures have never been greater and the high cost of drug development, coupled with the low sales potential of pediatric products creates barriers to industry's allocation of its own resources. Companies are increasingly risk averse in all business operations, including research. Companies are more likely to select CROs than PPRUs to conduct any pediatric studies which they decide to do.

PPRU Organizational Issues. PPRU investigators have relationships with companies and clinical knowledge which is respected by a small group of players in industry who know of their work. These players views PPRU management of families and children, the pragmatic approach of the investigators and the adverse event monitoring to be important assets of the PPRUs. Nurses are respected, blood sampling techniques appreciated and the speed of the research acknowledged. PPRUs are viewed as being able to deliver the "numbers" that companies need and the investigators are viewed as being better than the average academic.

Companies in the pharmaceutical industry are so essential to the success of product development that we have agreed they merit special consideration in our planning. **Companies have their own sets of issues with implications for pediatric research and development.**

The current environment is more favorable than in the past several years because of scientific developments, the presence of the PPRUs and the policy initiatives of FDA Commissioner Kessler. This is a window of opportunity, which will be time-limited but which can be extended through public policy communications, the institutionalization of FDA initiatives, strong management of the PPRU asset and the engagement of new PPRU partnerships with managed care.

Despite this, Pediatricians and pediatric populations are devalued markets. Few companies promote products in this area, most lack experience in pediatrics and are fearful of the costs and risks involved at a commercial level. Many children's advocates have confrontational styles and are not known for working cooperatively with industry. The additional ethical, regulatory and legal barriers are also substantial. As a result, pediatrics competes unfavorably against the larger, better known markets, products and disease areas.

Company Missions. Companies are driven by two missions -- first, to discover, develop and promote appropriate clinical use of products and second, to product returns for shareholders (since they are equity, rather than debt, financed). The development of pediatric pharmaceuticals is consistent with the first mission, but inconsistent with the second. This is a tension which must be carefully managed within companies. Advocates within companies will benefit from the NICHD, PPRU and FDA programs, but any progress they make will be slow and incremental.

Company Activities. Companies are focused on their objectives, which are measured, reported quarterly and annually, and which have a direct, personal impact on the jobs, salary and bonuses of the employees. Objectives are translated to financial implications and high-risk/low return projects (such as pediatric indications) rarely survive. Further, company advocates for pediatric drug development can be at personal risk if the support system created by the NICHD, PPRUs and FDA fails to perform.

Company Style. Companies operate in teams which are hierarchical, multidisciplinary and lateral. These teams and the relationships among the disciplines and people in them are very complex. Decisions are frequently consensus-based. Companies are risk-averse and retrenching, with numerous layoffs and budget cuts, including in research. Companies are highly disciplined and very well-trained. In their dealings with outsiders, they are very scripted and well-controlled in what they will commit. As a result, it will take longer than would be optimum for companies to decide to take action on any of its drugs. Company advocates will manage not only scientific and financial, but internal political dynamics to move projects forward. This process will be time-consuming and frequently frustrating.

Company Decision Dynamics. Pediatric products face a number of internal hurdles besides high risk/ low return economics. The *Research Division* of companies is product discovery and development driven (rather than population focused). It wants the best researchers available in the academic community but is unwilling to risk delays in producing results and will select CROs over academics in order to assure timely study completion. It is rare that companies will have internal pediatric advocates in Research, although some do exist. *The Marketing Division* resists pediatric labeling because so few companies promote to pediatricians that an indication has little current sales value. In order to attain sales of a product, the company will need to expand its sales and marketing infrastructure, a high additional cost unlikely to be offset by sales, especially when off-label use already guarantees some product sales. *Sales and Clinical Service Departments* would be required to develop new training and physician service programs and to manage additional Adverse Event Reporting. *Manufacturing* Divisions would be required to change packaging and expand inventories when a pediatric product is approved.

Attachment A
PPRU NETWORK DISEASE/CONDITION EMPHASIS

	LSU	CWR	UT	CMH	CHRF	ACH	UC	TOTAL
Analgesics	X	X		X				3
Antibiotics	X				X	X		3
Anticonvulsants					X			1
Antidepressants (adolescents)	X							1
Antihypertensives						X		1
Anti-infectives	X	X						2
Anti-inflammatories	X							
Antivirals							X	1
Asthma	X			X				2
Benzodiazapines	X				X			2
Cardiovasculars		X	X					2
Cystic Fibrosis	X						X	2
Detoxifying Agents					X			1
Diuretics		X				X		2
Endocrine Disorders							X	1
Fungicides					X			1
Gastrointestinal				X				1
Hepatic Drug Metabolism	X		X					2
Hypertension				X				1
Immune Suppressants							X	1
Metabolic Disease							X	1
Nutritional Maintenance							X	1
Oncology			X					1
Parenteral/Enternal Nutrition			X					1
Pharmacokenetics	X	X						2
Renal Disease			X					1
Sedatives	X	X						2
Surgery Premedication	X							1

PPRU NETWORK CAPABILITIES

	LSU	CWR	UT	CMH	CHRF	ACH	UC	TOTAL
Advertising Tag Line			X					1
Mission, Vision, Values	X		X				X	3
Overall Capabilities	X		X		---			2 (1)
Clinical Trials Management								
Develop Protocols	X	X	X	X	X	X	X	7
Develop Case Report Forms	X	X	X	X		X	X	6
Manage Investigator Identification	X	X	X	X	X	X	X	7
Manage IRB	X	X	X	X	X	X	X	7
Inpatient/Outpatient Facilities	X	X	X	X	X	X	X	7
Phase I Clinical Pharmacology	X		X	X	X		X	5
Collect/Review Regulatory Documents	X		X	X	X	X	X	5
Initiate New Site								
Store Drugs	X	X	X	X	X	X	X	7
Monitor Clinical Trials (in limited sites)	X	X	X	X	X	X	X	7
Monitor patients/Manage AEs	---	X	X	X	X	X	X	6 (1)
Archive/Track Data and Correspondence	X	---	---	X	X	X	X	5 (2)
Manage Data	---	X	---	X	X	X	X	5 (2)
Analyze Statistics	X	X	X	X	X	X	X	7
Assure Clinical and Data QA	X	X	---	X	X	X	X	6 (1)
Integrate clinical study reports	X	X	---	X	X		X	5 (1)
Prepare NDA Dossier								
Clinical Monitoring								
Select, qualify, train, manage existing sites	X	---	X	X	X	X	X	6 (1)
Motivate Sites			X	X	X	---	X	4 (1)
Recruit patients	X	---	X	X	X	X	X	6 (1)
Assess drug accountability	X	X	X	X	X	X	X	7
Monitor enrollment targets	X	X	X	X	X	X	X	7
Conduct close-out visits	X	X	X	X	X	X	X	7
Create data analysis plan	X		---	X	---	X	X	4 (2)
Implement data entry, validity, logic checks	X		---	X	X	---	X	4 (2)
Transfer compatible database to client								
Biostatistical Services		X					X	2
Consult on Design	X	X	X	X	X	X	X	7
Design Statistical Programs	X	X	X	X	X	X	X	7
Archive all programs	X		X	X	X	X	X	6
Secure Independent quality review							X	1
Utilize SAS software	X	X	X	X	X	X	X	7
Integrate summaries of safety and efficacy	X	X	X			X	X	5
Interface with FDA and client	X	X	X	X	X	X	X	7

	LSU	CWR	UT	CMH	CHRF	ACH	UC	TOTAL
Regulatory and Medical Affairs			X					1
Manage IRB	X		X	X	X	X	X	6
Prepare Regulatory Documents	---	IND	X				X	2 (2)
Liaison between clients and Regulators	X		X	X		X	X	5
Monitor Medical Care and AEs	X		X	X	X	X	X	6
Audit Clinical Quality	X	X	X	X	X	X	X	7
Manage central data archive			X		X	---	X	3 (1)
Manage Medical Communications	X	X	X	X	X	X	X	7
Financial/Accounting Support	X	X	X	X	X	X	X	7
Therapeutic Experience	X	X	X	X	X	X	X	7
Megatrial Experience	X		X			X	X	4
Project Management Experience	X		X	X	X	X	X	6
Post-Marketing Surveillance		---	X			X		2 (1)
Health Economic Protocol Design					X	X		2
International Experience	X	X	X		X		X	5
Publication Capabilities	X	X	X	X	X	X	X	7

Key: X Capability --- Some Capability