NATIONAL INSTITUTES OF HEALTH
AND HUMAN DEVELOPMENT

A PLAN FOR THE DEVELOPMENT OF PEDIATRIC PHARMACEUTICALS AND FORMULATIONS

INTRODUCTION

This report is an outgrowth of continuing efforts by the National Institute for Child Health and Human Development (NICHD) to promote and facilitate the development of pediatric pharmaceuticals and formulations. For the purposes of this report, pediatric pharmaceuticals and formulations refers to:

- Pharmaceutical and biological products developed specifically for preventive or therapeutic use in children, and
- Pharmaceutical and biological products not developed specifically for children, but for whom special formulations must be developed in order to facilitate preventive or therapeutic use in children.

This report does not include issues related to the development of medical devices and medical foods, although those issues may be similar to those in the development of pharmaceuticals and biologicals.

This report deals with those policy and political, NICHD, Pediatric Pharmacology Research Units (PPRU) and FDA organizations, and business and commercial issues can be addressed in the near-term to facilitate the development of pediatric pharmaceuticals and formulations. It is for that reason that the ethical, legal and cultural barriers to the development of drugs and biologicals for children, which will require longer-term considerations, are not discussed.

RECOMMENDATIONS

NICHD should broaden its current limited consideration of pediatric pharmaceutical development and redefine its objective as the *quality pharmaceutical care of children*. In doing so, it should pursue a four-part strategy:

- Promote pharmaceutical product development and quality care as a public policy issue.
- Support PPRU - Industry partnership management.
- Provide regulatory support. and
- Promote quality pediatric pharmaceutical care practices.

Of these, two are most important: PPRU support and Regulatory support.

Promote Pediatric Pharmaceutical Product Development and Quality Care as a Public Policy Issue

The NICHD should assure a continuing level of visibility on the issue of product development and quality care needs of children by encouraging, facilitating and funding conferences, exhibits, communications, electronic bulletin boards and publications on the subject. These communications should be addressed to all relevant audiences: clinicians, parents, health care payers, pharmaceutical companies and investigators. These communications should be consistent with the priorities and objectives of the institute as noted in the PPRU - Industry Partnership recommendation below.

Public policy issue promotion is the foundation on which resource allocations are made in both the public and private sectors. It facilitates initial government investment and, eventually, commercial market growth. Since pediatrics does not yet represent a substantial commercial market, it is public policy which will be a key driver of initial NICHD success in achieving pediatric pharmaceutical development and PPRU utilization.

Issues such as this one receive attention in cyclic patterns and significant progress is made each time the attention peaks within a favorable environment. It appears that the issue of pediatric pharmaceuticals is at or near its peak at this time. As such, it is important that NICHD capitalize on the naturally-occurring events in the environment (in particular, Commissioner Kessler's tenure with at the FDA). Since it is harder to create momentum where there is none than it is to utilize the existing momentum, the next 8-12 months may be particularly favorable.

The community of people and resources devoted to this issue is small in comparison to other issues competing for time and funds. As a result, the orchestration of communications through the press and in broader forums is necessary to create a presence for the issues which is greater than the small community can create through its personal presence. This method of policy communications is also very cost-effective and the NICHD has a number of existing mechanisms for communications which can be used.

Any attention to this issue will wane as 1996 Presidential Campaign politics receives increasing coverage, and NICHD should not try to compete for airtime during the heaviest months of campaigning. However, immediately after the election, NICHD should return to a higher level of sustained communications to extend the "peak" attention period for as long as possible.

Support PPRU - Industry Partnerships

NICHD should clarify its objectives regarding pediatric pharmaceutical development and PPRU-based studies. Is the goal to conduct studies on all approved medications or only selected products? All investigational drugs or only selected products? All medications in a class or only selected drugs? All single-source medications or only selected drugs? All multi-source drugs or only selected versions? Drugs produced by all companies or only some companies? Drugs for all disease targets or only some diseases?

In both oral and written NICHD communications, the objectives of this project are stated in both limited (targeted drug development) and expansive (all drugs development) terms. A clear statement of objectives will enhance NICHD communications on this subject.

NICHD should select priorities from among its objectives and should target its promotional efforts on those targets.

If the NICHD chooses a more expansive objective, it should organize those objectives into short- and long-term timeframes and will achieve greater success if it focuses on a more limited set of drug and company targets. The large number of drug and company targets might appear to be helpful in achieving a match between projects and PPRUs. In fact, however, companies can be more responsive to specific, focused requests. In addition, focusing will make it easier for NICHD and/or the PPRUs to prepare for company meetings.

NICHD should adopt an active project management approach, using project management techniques.

At this stage of PPRU funding, NICHD should actively manage the tasks required to succeed in placing studies in the PPRUs. PPRU principal investigators must be involved as well, but the need to place studies in the PPRUs as soon as possible requires centralized management that only the NICHD can provide.

NICHD should view PPRUs as a product/service they have developed and companies as customers who may be interested in purchasing those products/services. NICHD and PPRUs should adopt a customer-focused sales and management approach to communications, relationship building, performance and service.

NICHD has placed itself in the position of the developer of a product (the PPRU) to meet a perceived market need and, at this point, is experiencing less than the success it anticipated.

NICHD could benefit from a more traditional, customer-focused sales approach. This approach is described in detail in this report. Once the “sale” is made and a company elects to place studies in the PPRU, NICHD and the PPRU should assure that all performance measures are met, that relationships are built and deepened and that any customer service problems are quickly resolved. In addition, since all products must be continually improved to remain successful in the marketplace, NICHD and the PPRUs must monitor its competition and company customer wants and needs. They must continually adapt the PPRUs to address those needs.

NICHD should not assume a leadership role in pursuing policy resolution of financial barriers to company investment in pediatric pharmaceuticals.

Policy discussions of financial disincentives to the development of “orphaned” products frequently note the following proposals to remove those barriers: tax credits for studies, market exclusivity for a particular indication, extended market exclusivity for all indications and waivers of FDA user fees.

For some small companies, the tax credit and user fee waiver proposals may be effective incentives. For all companies, the extended market exclusivity for all indications would be effective.

It is unlikely that the public policy climate is ripe for any of these changes and the NICHD would greatly dilute its resources to pursue the internal Administration and Congressional consensus any change in financial incentives would require. NICHD should be alert to opportunities to expand on similar initiative by other interest groups but should not take on the leadership role itself at this time.

Provide Regulatory Support

NICHD should engage in discussions with Commissioner Kessler to determine how best to institutionalize the changes he has initiated in the FDA to facilitate pediatric product review and approval.

Commissioner Kessler's personal interest in pediatric pharmaceuticals is well known and his leadership within the Agency has been effective in creating a favorable environment for change. A new regulation, new approaches to pediatric labeling, a new coordinating committee are signals to investigators and companies that the regulatory *may* be more favorable for pediatric product development and approval.

Unfortunately, this interest has been personalized to the Commissioner, a political appointee whose term is limited and unknown. Without institutionalized change, companies will be unlikely to shift their priorities to focus on pediatric drugs, fearing the agency's priorities will change when a new Commissioner is appointed.

NICHD and FDA should jointly monitor the experience of the Pediatric Drug Committee and should seek expedited, high-level problem resolution when necessary.

NICHD should monitor the experience of companies submitting applications for review and engage the FDA in appropriate systems-level discussions of problems (NICHD should not intervene in any discussions between a company and the FDA).

Individual reviewers make the most important determinations about medications, regardless of the Commissioner's interests and priorities. At this point, a few champions in selected companies trust recent FDA regulations, committees and speeches enough to risk moving forward with pediatric product review applications.

They have selected product test cases to judge whether FDA reviewer actions will be consistent with policy statements. If these test cases receive the treatment anticipated by the policy statements of the agency, more pediatric studies will result. If not, the negative response of companies will dampen interest and set this issue back by several years. Monitoring of outcomes and intervention to assure success will be important activities of the NICHD.

Neither the NICHD nor PPRU should intervene with the FDA on a drug-approval matter. Companies are tightly organized and accountable in their dealings with the FDA. With so much of the business at stake, anyone outside the company must be careful not to speak with the FDA on any matter related to its products.

If FDA is inclined to provide funding in this area, NICHD should encourage that FDA funding be used to sponsor educational, awareness and information meetings and publications and for the resolution of clinical barriers.

In the past, the FDA has provided clinical trial funding in orphan drugs. This program was effective in stimulating the development of drugs for rare diseases, but mainly in those situations where small companies were developers of the products.

Since it is most likely that the largest share of the target products will be owned by major firms for whom clinical trial financing is not the major barrier, such financing will not be the best use of resources. Funding which raises awareness, generates solutions to technical and scientific challenges to development and establishes standards for drug development in children are more likely to positively affect the objectives of the NICHD.

FDA should train NICHD and PPRU investigators in the regulatory requirements for studies and issues in product review so that these individuals are better prepared for discussions with companies and the assistance they will provide to companies.

Companies are more experienced than NIH and academic investigators in dealing with the FDA through the product development, review and approval phases. As a result, the NIH and academic investigators are at a disadvantage when compared to their competitors for study placements – Contract Research Organizations – many of which are staffed by former company scientists and executives. The ability of NICHD and the PPRUs to "talk the talk" of the FDA will reassure companies that the PPRUs are a qualified partner sensitive to their needs.

Promote Quality Pharmaceutical Care in Pediatrics

NICHD should review all the phases of pediatric pharmaceutical care and expand its activities to include the promotion, prescribing and adherence in the use of medications.

PPRUs were established to eliminate one of the important barriers in the development of pediatric pharmaceuticals.

Barriers are often viewed sequentially, and the PPRUs were the logical next step in the profession's pursuit of more drugs for children. Even successful operation of the PPRU program and use of the PPRUs by industry will not achieve NICHD's goal – appropriate pharmaceutical care of children – as other steps remain. It is for this reason that a broader objective is recommended.

A broader perspective that considers the entire scope of needs and requirements of children for pharmaceutical care can engage the resources of new allies – particularly managed care – and find new methods – formulary preferences, for example – to accomplish NICHD objectives.

CONCLUSION

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 partners in managed care.

NEXT STEPS

The steps remaining in this project include:

- Confirm (and revise as needed) recommendations
- Refine Action Plans
- Refine company R&D organization charts
- Assess any clinical barriers
- Refine assessment of CRO competition
- Develop PPRU sale specifics in conjunction with NICHD and/or PPRUs

PEDIATRIC PHARMACEUTICALS DEVELOPMENT

ISSUES	THREATS	OPPORTUNITIES
Ethical	• Human subject concerns	• Duty to care • Equity in care
Legal	• Current and future civil liability • History of AE's in pediatric use	• Standards of care
Cultural	• Children not visible or powerful • Children not a viable medical market	
Policy & Political	• Children's advocates not successful; use attack strategies • Issues are cyclic, peak now - trough later • Competition for other resources: other diseases, other economic sectors, other generations	• Peak of interest cycle, convergence of science and regulation
FDA Organizational	• Company - FDA relationships fragile • FDA initiatives; Pharmacoeconomics, advertising • Reviewer-based accountability	• Commissioner personal support • Pediatric Development Committee • FDA review of common drugs for children
NICHD Organizational	• Mixed track record of drug development • NIH-FDA culture conflicts • NIH-company culture conflicts • Academic-company culture conflicts	• NICHD focus on PPRU
Business/Commercial Organizational	• High development and marketing costs - low sales and income return • Pediatric indication spillover to adult market slows approval • R&D competition - other drugs, other researchers, CROs • Downsizing, coordination costs high • Risk-averse culture	• Generic firm transition • Biotech firm reemergence • Pharma firm niche interest
PPRU Organizational	• Overlap • Competition	• PPRU sales skills • Multicenter capacity • Knowledge/skills of PIs