



July 29, 2004

Janet Woodcock, MD
Acting Deputy Commissioner
For Operations
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20852

RE: Challenge and Opportunity on the Critical Path to New Medical Products

Dear Doctor Woodcock:

As you are aware, The American College of Clinical Pharmacology (ACCP) is a premier professional Society representing clinical pharmacologists across the Country and world. In response to the Food and Drug Administrations (FDA) recent publication of the draft document entitled "Challenge and Opportunity on the Critical Path to New Medical Products" the College's Executive Committee formed a sub-committee of senior investigators and practitioners with well established expertise in study methodology, design and execution and data analysis, for both pediatric and adult clinical trials, to review this document and provide recommendations. Serving as the subcommittee's chair, I am writing you on behalf of the College to provide some recommendations for your consideration regarding this most daunting challenge.

We applaud the Agency's efforts in addressing the important, timely and complex issues surrounding new medical products development in an era witnessing unprecedented advances in the basic and clinical sciences. The draft Critical Path "white paper" is an excellent consensus document outlining the strengths but more importantly the many limitations and weaknesses that exist in our current approaches to new product development. This "white paper" is an excellent proposal for and stimulus to the drug development, regulatory and clinical academic stakeholder communities to assess current gaps in our understanding of how best to evaluate new medical entities. It is also a "wake-up call" for the scientific and pharmaceutical communities to recognize the need for change in the manner by which it evolves information into decisions so that the cost of drug development is less of a burden to the US economy, which now fuels the world's access to new medicines. The Agency is to be commended for their expert, comprehensive assessment of the many complex issues surrounding the "pipeline problem" and compiling these data into a concise and clearly worded document. We agree

completely with the FDA's position that "A new product development toolkit – containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques - is urgently needed to improve predictability and efficiency along the critical path from laboratory to commercial product". Below, I have summarized recommendations from our ACCP subcommittee and the College's Executive Committee that we respectfully submit for your consideration as this document undergoes review.

General Comments

1. We believe this document will achieve its goal of stimulating reassessment of and focused research into the development of new "toolkits" to address the challenges of efficient navigation through the critical path. Of immense importance to this end are the opportunities the FDA has in critically assessing their vast amounts of data within the Agency's databases that encompass the spectrum of human and veterinary diseases, their therapeutics, their tolerability profile and study. The "white paper" appropriately addresses these facts and opportunities. However, the uniqueness of such a database and its wealth of multifactorial interrelationships across disease states and drug classes suggest the need for a priority status and ongoing, continuous assessment. Such an Agency initiative could be fostered by the establishment of a separate section or identified program within the Agency comprised of experts in clinical pharmacology, biostatistics, pharmacokinetic (PK) – pharmacodynamic (PD), pharmacogenetic / genomic and proteomic modeling whose sole purpose is to mine and disseminate data pertinent to the critical path development. This program's work could be guided by the Agency's "Critical Path Opportunity List" as well as from outside experts in specific areas. One approach to accomplish this task and to define prioritized agendas might involve an additional charge by the FDA to their select FDA Advisory Committees. These already in-place structured Committees could work closely with this new "program" of the Agency in identifying specific information gaps within their field(s) of expertise, provide prioritization recommendations of tasks, direction and consultative interpretation of the findings. More importantly, specific Guidance / white paper documents could be prepared and then reviewed by the specific Expert Committee members with FDA staff assuring contemporary and future applicability without compromising any confidentiality commitments as the Committees would only see aggregate data absent of all identifying qualifiers. Alternatively, the Agency could establish a new FDA Expert Committee in partnership with Pharma and other industry sponsors and academia. Select failures would undergo specific root cause analysis to attempt to identify what variables contributed to the failure, including a thorough analysis of the multiple issues in preclinical, clinical, regulatory, business, manufacturing, etc. This analysis could be mapped against successful development molecules for a thorough understanding of the issues behind the increasing percentage of failures occurring later in drug development. Regardless of the process selected, the amount of precious, real-world drug development success and failure experience that can be gleaned from this database is immense and should represent an Agency priority.
2. Related to the above, we believe the FDA has served and should continue to assume the leadership role in providing "Guidance" for the need for biomarker/ surrogate marker identification and validation expanding upon the current Guidance document, i.e. "Guidance for Industry: Exposure-Response Relationships". Indeed, the area of surrogate endpoints and their validation is a critical issue that appears too often to be addressed on an *ad hoc* basis. Pharmaceutical sponsors seem to "solve" such problems for their current development program, but the validations are proprietary and thus, uninformative for other sponsors. This would seem to represent another area where intervention could take place. Support for the

generation and validation of surrogate endpoints is in everyone's best interest. It is important to investigate the establishment of mechanisms whereby academics and industry, in concert with government could collaborate on the development and validation of such surrogate endpoints and have the validated endpoints publicly available. This could be done through grants from Federal Agencies, either directly, or through users fees paid by sponsors seeking an NDA in a specific area.

3. There is a sense that uncertainty exists among many stakeholders regarding specific FDA requirements, particularly as it relates to product tolerability / safety. It is our opinion that whenever possible the Agency should strive to provide specific definitions for "acceptable frequency rates" for specific drug classes. With such definitions stakeholders can better design their studies that captures, with a reasonable degree of certainty, specific adverse effects. The same need for defined frequencies could be made for specific surrogate marker / biomarker targets. These target frequencies could be derived from the ongoing assessments of the FDA's database as described above (general comment #1) and refined with each new entry within a specific class. Moreover, incentives might be developed to encourage innovative research designs. One possible approach might include restructuring of the patent modifications or FDA review time boundaries for new classes of therapeutic agents or new members of a class representing new therapeutic advantages vs. simply "me-too" drug applications. We appreciate the complexity of determining such definitions but believe that some frequency boundaries could be determined by the FDA and sponsor during the development process.
4. The FDA Orphan Drug Program has been and continues to represent a highly visible major, successful initiative that has borne enormous results from limited resources. The Agency should develop additional funding mechanisms / programs to support research proposals focused on the critical path. The Agency might establish an additional funding program for the competitive selection and award of grant funds for proposals that focus on innovative approaches to addressing critical path challenges including the infrastructure and economic drivers within a pharmaceutical company that create costly inefficiencies. New practices and habits within a drug development paradigm must evolve in parallel with the incorporation of any "new tools" identified. We believe the process of such a focused research grant program should reside within the FDA and not be delegated to the NIH as the Institute's research focus is largely basic science. Further, where within the NIH such a research initiative would reside could be difficult to identify. Ideally, the NIH infrastructure could partner with the FDA with regard to budget contributions as well as expert reviewers.

Specific Comments

1. Page 2, Figure 1: The research and development (R&D) spending might be detailed here such that a focused assessment of costs and expenditures could be made. It appears that while R&D costs have risen over the past 10 years, the actual R&D spent during this same timeframe has remained relatively constant. It appears that the costs associated with early branding and otherwise marketing costs have often times been consolidated into R&D costs increasing the apparent overall R&D cost.
2. Page 2, paragraph 1: It would appear that many of these "cumbersome assessment methods" have been used to satisfy current regulatory requirements for registration. We believe that greater flexibility by the FDA should be exercised in the consideration of alternative endpoints, surrogates, and biomarkers or the problem of traditional assessment methods will continue to be employed. The FDA should more aggressively, on a continuous basis,

continue to foster an environment that provides incentives for innovation. This would most likely require that FDA actively participate in facilitating the validation of tools to predict a drug's effectiveness and safety, and in developing surrogates for outcomes that will speed the later stage development timelines and reduce costs enormously. (please see general comments 1 and 2 above)

3. Page 3, 1st paragraph: It would appear that attempting to link any association of the human genome sequencing with the timelines on availability of new medicines may be a bit over-reaching. Such a realization will take some time. The value of the “white paper” as a stimulus might be strengthened by expanding the discussion here to include strategies embracing the path forward from human genome sequence to clinical application of the information. An interesting component of this discussion could focus on what the FDA believes is the “practice” or development “habits” that are lacking in order to best exploit this data.
4. Page 3, paragraph 3: As stated above in our General Comment #1 above, Agency reviewers see the complete spectrum of successes and best practices during clinical trials, as well as the failures, slowdowns, barriers, and missed opportunities that occur during product development. The agency is in a unique position to make available the enormous databases from pooled data across studies, programs and pharmaceutical companies. Are steps in this direction envisaged?
5. Page 3-4, paragraph 2 and (Figure 3): It would appear that most of the increase in development costs over the last 5-10 years can be attributed to Phase II/III development, underscoring the critical need to develop better tools and predictors of safety and efficacy in Phase II, and innovative / less cumbersome clinical endpoints in Phase III. As noted above in General Comment # 2, the FDA is in a unique position to proactively partner with industry and academia to develop and validate new tools and endpoints against accepted current standards, and incorporate these innovations in a timely manner into the individual registration guidelines. Defined variables and study strategies must be completely available for public access. Sponsors may often interpret select, current FDA guidelines for development as onerous; the Agency is in the position to drive consensus on the acceptability of new tools and endpoints that could drastically improve efficiency in the drug development process.
6. Page 4, Figure 3: An important missing detail in this figure is the fact that the type and number of studies within each of these timeline categories has changed. Interestingly, more has not been better. The recent era has been more appreciative of drug interactions and special populations with legislative incentives prompting new responsibilities around caution. Such an environment would appear to influence critical path decisions. In addition, the influence of advertising has created an extremely aggressive and competitive marketing environment in which scientists are influenced at a much earlier stage regarding perceived (or real) compound weaknesses (drug interactions, dosing more frequent than QD, etc.). The refinement of strategies to better screen compounds in these early stages is also needed.
7. Page 5, paragraph 3: The statement here seems to suggest that the increased basic biomedical knowledge is able to produce more candidates for successful development. The fact that this is not the case, however, suggests that this is not only due to “outdated” tools in development or translational medicine but continued large gaps in basic biomedical knowledge.
8. Page 6, Figure 5: The figure shows approximate timing of the various R&D categories but does not provide adequate detail for translational and critical path research categories. The

impact of this figure may be enhanced with expansion to include more detail, if it is available.

9. Page 8, 1st paragraph: The likelihood estimates for ultimate success based on phase I entry are very striking. Additional discussions addressing reasonable targets for phase I success beyond the cost savings might enhance the impact of this section. A more thorough evaluation of the “biomedical breakthroughs” referenced throughout the document seems warranted in order to convince readers that their implementation should result in development efficiency expectations.
10. Page 8, paragraph 2: This is indeed a critical goal that all stakeholders should strive to achieve. A major hurdle for incorporating new tools and technologies is the lack of correlation with accepted endpoints and outcomes. Risks to successful development and registration exist if the endpoints used in Phase I-II for establishing proof-of-concept and assessing safety do not correlate with or are not predictive of the endpoints used in Phase III and necessary for registration. As addressed previously, “FDA scientists are uniquely positioned” to see complete information from various sources, there should be opportunities to capitalize on databases that exist at FDA to analyze and validate new tools for use in drug development. In addition, FDA could help to actively facilitate the validation of new technologies for safety and efficacy assessments by bringing together industry and academia partners to a) conduct comprehensive meta-analyses of existing information, and/or b) commission epidemiologic studies/programs, such as the Osteoarthritis Initiative, to address critical gaps in the tools needed for drug development in high priority areas.
11. Page 8, paragraph 2: The goal of the critical path research should be more informative clinical trials and not “the tools”. If we only deliver tools, we have no guarantee of a public health benefit.
12. Page 9, paragraph 3: Failure to demonstrate medical utility is especially costly in indications where large patient numbers and long observation times are required to satisfy current regulatory guidances. It is critically important to identify good short-term predictors of the long-term clinical outcomes, which could be used as a basis for initial registration, perhaps with a Phase IV commitment to provide additional longer-term data, or used as an indicator for early termination due to futility, thus reducing additional costs. In addition, positive evidence based on surrogate marker results should also count as evidence together with the direct evidence based on the clinical endpoint. It would be helpful if guidance to this respect would be more specific.
13. Page 11, 1st paragraph: The issue of rebuilding the relevant disciplines is critical. It is also reasonable to expose the needs in certain areas as extreme and require investment in addition to revision. These disciplines also need to be better integrated at the education level. This is reflected in several new NIH initiatives (training the workforce of the future) and should be highlighted as well.
14. Page 11, paragraph 2: More emphasis should be placed on “Proof of Concept” trials and development of adequate tools to predict safety and efficacy (see above), since in many therapeutic areas, the largest costs are incurred in Phase IIb and Phase III development. This will require collaboration with statisticians and modeling experts to develop pharmacostatistical models of drug efficacy and safety using simulation software. There is an opportunity to enhance the impact of such studies if all information is used, including the following powerful tools: stochastic optimal design, population PK modeling, MAP-

Bayesian estimation, linkage of exposure to response and Monte Carlo simulation for dose identification, to mention a few.

15. Page 16, 1st paragraph: The point regarding disease-specific trial design and endpoints assessment needs to be more prominent here. As stated it appears as an afterthought. This clearly is part of the ultimate goal assuming the new toolset is in place.
16. Page 18: The FDA report card sections are good and definitely speak to the agencies commitment to this topic. However, the descriptions lack the detail required for a reader to further investigate. A more quantitative description with appropriate references would be helpful. This goes for the “opportunities” discussed throughout. It is also reasonable to reference many industry-led initiatives in these areas as well.
17. Page 19, paragraphs 2-3: Several opportunities are noted here, namely targeted research of specific toxicity problems guided by proteomics and toxicogenomics, and “in-silico” computer modeling (predictive toxicology) to mention a few. Data mining as commented upon in General Comment #1 incorporating existing clinical data could help to construct models to screen candidates in future developments. Additional possibilities appear to include: the identification of safety markers (the document mentions biomarkers primarily in the efficacy context), a focus to identify more systematically when in-vitro and animal models allowed for a correct prediction and when not have never reached FDA. As stated in General Comment # 1 above, the value of critically analyzing drug development failures in combination with the successes cannot be overemphasized.
18. Page 21: The statement that automated blood pressure monitoring makes a placebo control unnecessary seems surprising. Such monitoring can reduce the within patient variability and could reduce sample size but does not appear to be able to remove the primary reasons having a placebo control. Also this statement seems in conflict with the respective FDA guideline for trials in hypertension. This issue might be expanded here including rationale for better reader understanding.
19. Page 30, 1st paragraph: The section on the Orphan Grant program is informative. It definitely has appeal for a possible test bed for the proposed new toolset. As stated in General Comment # 4 above, is it possible to expand this program to embrace “Critical Path” issues?
20. Page 30-31: Regarding next steps (and throughout) this document appears to focus only on US-based stakeholders. It is unclear if this is intentional or an oversight. Either way this topic should be addressed. It would appear that some plan for involving the “global medical community” even at these very early stages, would be beneficial to the design of the new “tool kit”.

I submit the above comments for your consideration on behalf of the working committee of the ACCP. We hope the above comments will be of value to you and your colleagues as the final editing of this important document goes forward. We again applaud the FDA for their efforts in bringing such an important issue to the forefront. If you or any of your colleagues believe that the ACCP may be of any assistance with this important task, please do not hesitate to call upon us.

Sincerely,

A handwritten signature in black ink that reads "Michael D. Reed". The signature is written in a cursive style and is underlined with a single horizontal line.

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cc. Robert Temple, M.D.