



Date: July 29, 2004

Dockets Management Branch  
(HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Docket Number 2004-N-0181

Response to FDA Call for Comments  
Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products

Dear Sir or Madam:

Reference is made to your March 2004 report on activities that could reduce hurdles in medical design and development of new drugs entitled "*Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products.*"

AstraZeneca shares FDA's concern over the decreasing number of new drugs approved in recent years and welcomes the Agency's initiative to join with its stakeholders to think creatively about translational research and its potential impact on pharmaceutical development and the regulatory review process. We appreciate that the report advances FDA's mission to promote medical innovation communicated in the 2003 FDA Strategic Plan. AstraZeneca has provided the attached document containing general comments and specific suggestions for improving the efficiency of nonclinical, clinical, and CMC "critical path" elements of pharmaceutical development.

Please direct any questions or requests for additional information to me at 302-886-5895.

Sincerely,

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Enclosure

2004N-0181

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**Comments from AstraZeneca on the FDA report entitled  
“Innovation/Stagnation: Challenge and Opportunity on the Critical  
Path to New Medical Products”  
(Docket Number: 2004-N-0181)**

**General Comments**

The FDA document addresses the observation that the pace of development and registration of new pharmaceuticals has slowed in recent years and indicates that a reason for this observation might be that new technologies and strategies arising from recent advances across the scientific and biomedical frontiers have been slow to be incorporated into drug development, with the result that *‘... developers have no choice but to use the tools and concepts of the last century to assess this century’s candidates.’*

The paper recommends: *‘A new product development toolkit – containing powerful new scientific and technical methods such as animal and computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques – is urgently needed...’*

The paper also describes FDA’s view of its role in accelerating the productivity and efficiency of pharmaceutical development and indicates a new FDA initiative to *‘... identify and prioritize (1) the most pressing development problems and (2) the areas that provide the greatest opportunities for rapid improvement in public health benefits.’* and that *‘This will be done for all three dimensions along the critical path – safety assessment, evaluation of medical utility, and product industrialization.’*

The paper, while identifying a number of areas of need, presents a relatively limited perspective of the challenges encountered to successfully register new pharmaceutical products. For example, the paper does not address the following:

- The impact of new guidelines and regulations to add additional required studies and investigations before a product may be registered (e.g., additional studies in juvenile (and potentially geriatric) animals to support newly required clinical studies sub-populations). While few disagree with the overall intent of making pharmaceuticals safer for clinical subpopulations, the additional studies require additional time and resources.
- While much has been done to harmonize international requirements for pharmaceutical development – such that specific studies may be conducted once and be ‘fit for purpose’ in the three major territories (US, Europe, and Japan), sponsors must continue to ‘think globally’ to eliminate remaining conflicts that require duplication (and even triplication) of studies. For example, under its Special Protocol Assessment procedures, FDA permits sponsors to submit their plans and protocols for nonclinical carcinogenicity evaluations for accelerated review by the Executive Carcinogenicity Assessment Committee (ECAC), and receive agency concurrence with the proposed programs and individual study

designs. What assurance is there that European and Japanese authorities will accept the ECAC concurrence and not place additional perspectives on these designs, requiring duplication of the most time consuming and expensive of non-clinical studies? This is one example of where harmonization across regulatory agencies would be particularly valuable.

### **Preclinical, Clinical, and CMC Hurdles**

FDA should classify identified hurdles as preclinical, clinical, or manufacturing-related. Within each sub-group FDA should evaluate the identified hurdles based upon prevalence across the industry, as well as the financial impact on the healthcare system, consumer, and industry. The timeframe for implementation should also be considered.

### **Nonclinical Aspects of Pharmaceutical Development**

From FDA's paper it is clear that the nonclinical biological aspects of pharmaceutical development represent only a small fraction of the resource expended on the 'critical path', and that this component has been quite stable over the past decade. The two aspects of the nonclinical program that are considered 'critical path' are those directed at predicting the eventual efficacy and safety profiles in humans and specific therapeutic populations, including aspects dependent upon age, gender, ethnicity, and underlying disease. A recent paper by Olsen et al (Reg. Toxicol. Pharmacol 32:56-67, 2000), suggests that the overall concordance rate for the safety profile developed using both a rodent and non-rodent species with the subsequent safety profile developed in humans was ~70%, suggesting that only ~1 in 3 new drugs should fail in clinical development due to unanticipated safety concerns. As the FDA paper points out, the true failure rate appears to be much higher, suggesting that the greatest area for improvement for nonclinical 'critical path' studies should be in predicting efficacy.

Included in the table below are some specific suggestions for improving the efficiency of the non-clinical 'critical path' aspects of pharmaceutical development:

<b>Hurdle</b>	Nonclinical testing that contributes little or nothing to current clinical safety profiling.
<b>Rank</b>	1
<b>Application (drugs, biologics, ?)</b>	All
<b>Therapy Area</b>	All
<b>Proposed Solution</b>	Agency/industry/academia review of all required nonclinical test paradigms to evaluate contribution to pharmaceutical

	development.
<b>Timeframe (years)</b>	2.5
<b>Roles</b>	Agency leads; industry and academic must contribute.
<b>Comments</b>	Goal is to eliminate testing that no longer adds value and to identify and prioritize improvements for remaining nonclinical testing.
<b>Hurdle</b>	Targeted/limited clinical pharmacology assessments w/o standard nonclinical packages.  FDA needs to commit to implementing the concept of screening INDs across Divisions in order to support specific clinical pharmacology and hypothesis (proof of principle) testing with compounds that are not likely candidates for eventual registration.
<b>Rank</b>	1
<b>Application (drugs, biologics, ?)</b>	All
<b>Therapy Area</b>	All
<b>Proposed Solution</b>	Identify nonclinical strategies that provide data to accelerate clinical 'proof of principle' (POP) testing.
<b>Timeframe (years)</b>	2.5
<b>Roles</b>	Agency leads; industry and academic must contribute.
<b>Comments</b>	Obtaining early correlation of POP endpoints between nonclinical and clinical models is key to eliminating failures due to lack of anticipated pharmacodynamic activity. While new technologies offer new opportunities with which to monitor PD endpoints, 'last century' nonclinical requirements greatly slow the rate with which experimental drugs may be evaluated for POP.
<b>Hurdle</b>	Efficiency in Agency responses to Sponsor queries
<b>Rank</b>	1
<b>Application (drugs, biologics, ?)</b>	All
<b>Therapy Area</b>	All
<b>Proposed Solution</b>	Identify mechanisms to accelerate Agency responses to Sponsor questions regarding Agency expectations. Specifically, increase interactions that fall outside of the routine regulatory meetings (Pre-IND, EOP2 and Pre-NDA).
<b>Timeframe (years)</b>	1-2
<b>Roles</b>	Agency leads (intra-agency issue)
<b>Comments</b>	With the exception of Special Protocol Assessments, Agency responses to specific Sponsor questions regarding nonclinical issues are variable, in our experience taking up to a year or longer. The reasons for such protracted response times are unclear and delay development decisions.

<b>Hurdle</b>	Harmonization of animal welfare standards and experimental endpoints for nonclinical 'critical path' studies.
<b>Rank</b>	1
<b>Application (drugs, biologics, ?)</b>	All
<b>Therapy Area</b>	All
<b>Proposed Solution</b>	FDA should engage with international agencies, industry, and academia to agree upon minimum standards for animal welfare (caging requirements, psychological supplementation, etc.) and critical endpoints (maximum tolerated dose [MTD]) to insure that individual nonclinical studies can be conducted to requirements in any of the 3 territories, and be 'fit for purpose' for approvals/registrations in the US/EC/Japan.
<b>Timeframe (years)</b>	2-5
<b>Roles</b>	Agency leads; industry and academic must contribute
<b>Comments</b>	<p>Pending changes in animal welfare requirements in the EC raise the specter that nonclinical studies conducted outside of EC and to local standards may not be 'fit for purpose' to support EC registrations.</p> <p>We have several examples where study endpoints (MTD), collected in compliance with EC regulations, were not acceptable to FDA and required repetition of studies.</p>
<b>Hurdle</b>	Clarification of acceptable biomarkers and their applications.
<b>Rank</b>	1
<b>Application (drugs, biologics, ?)</b>	All
<b>Therapy Area</b>	All
<b>Proposed Solution</b>	Develop a comprehensive list of biomarkers deemed 'acceptable' by FDA and their applications. Develop specific criteria (with examples) for identification and 'validation' of new biomarkers.
<b>Timeframe (years)</b>	1-2
<b>Roles</b>	Agency leads; industry and academic contribute
<b>Comments</b>	The FDA paper emphasizes the role of biomarkers for acceleration of pharmaceutical development – it would be extremely helpful if FDA would provide a listing and status of currently acceptable biomarkers and criteria for establishing new biomarkers.
<b>Hurdle</b>	Lack of consistency on requirements between Divisions within FDA contributes to nonclinical study failures and repetition of studies
<b>Rank</b>	1
<b>Application</b>	All

<b>(drugs, biologics, ?)</b>	
<b>Therapy Area</b>	All
<b>Proposed Solution</b>	
<b>Timeframe (years)</b>	1-2
<b>Roles</b>	Agency leads; industry and academic must contribute
<b>Comments</b>	The CAC and Special Protocol procedures provide a model for standardization of study requirements and responsiveness regarding carcinogenicity assessments across divisions. Can this model be expanded to include requirements for genotoxicity, juvenile animal studies, etc.?
<b>Hurdle</b>	Time and resource to produce nonclinical study reports in compliance with GLP requirements
<b>Rank</b>	2
<b>Application (drugs, biologics, ?)</b>	All
<b>Therapy Area</b>	All
<b>Proposed Solution</b>	FDA is currently working to co-develop with industry standards for electronic nonclinical data (SEND), in conjunction with a parallel effort to develop standards for electronic clinical data. With completion and implementation of SEND, sponsors will have the option to provide FDA with all of the required nonclinical regulatory toxicology datasets in electronic format. Presumably, the SEND datasets are fully GLP compliant and certified (as currently so for paper datasets). In order to encourage sponsors to provide complete nonclinical toxicology data sets in SEND (GLP compliant) format, consider offering this option IN PLACE OF current GLP-certified study reports.
<b>Timeframe (years)</b>	3-7 (requires implementation of SEND)
<b>Roles</b>	Agency leads; industry and academic must contribute
<b>Comments</b>	If sponsors are going to provide full GLP-certified SEND-compliant non-clinical datasets, it is redundant to also require the GLP-certified study report, and the cost of development could be reduced by permitting sponsors to provide one or the other, but not both.

## Clinical Aspects of Pharmaceutical Development

Included in the table below are some specific suggestions for improving the efficiency of the clinical 'critical path' aspects of pharmaceutical development:

<b>Hurdle</b>	Difficult to enroll sufficient patients in a timely fashion for low incidence conditions.
<b>Rank</b>	1
<b>Application (drugs, biologics, ?)</b>	Target patient populations where incidence is sparse
<b>Therapy Area</b>	Anti-infectives (all classes)
<b>Proposed Solution</b>	Consider expansion of Federal Register 67: 37988-37998, May 31, 2002 (Final Rule; 21 CFR 601.90-95 [biologics] and 21 CFR 314.600-650 [drugs]), to permit demonstration of efficacy in one (or more) well-controlled animal models/studies to substitute for clinical efficacy studies, with appropriate demonstration of acute/subacute safety and exposure in human volunteers.
<b>Timeframe (years)</b>	1-2
<b>Roles</b>	Agency leads; industry and academic must contribute
<b>Comments</b>	One of the obstacles preventing broader development of new anti-infective strategies is the difficulty and expense in conducting 'last century' clinical efficacy studies for infectious agents. These design issues often present difficulties for enrolling patients. This problem has become acute with the need to develop new strategies for bioterrorism agents (e.g. anthrax), resulting in FR 67 and the so-called 'animal rule'. We propose a limited expansion of the 'rule' to stimulate development of anti-infective agents.
<b>Hurdle</b>	The critical path document only focuses on poor application of new technology within drug development; there is little reference to current FDA policies and procedures that have contributed to the stagnation over recent years. For example, in cancer and infection, the current FDA stance on non-inferiority trials is preventing progress; in the worst-case scenario, this stance prevents registration and, in the best-case scenario, complicates registration of novel anti-cancer therapies that are as effective as cytotoxic chemotherapy but are much better tolerated. In infection, this stance has driven many companies out of investing in infection R&D.
<b>Rank</b>	1-2
<b>Application (drugs, biologics, ?)</b>	All drugs and biologics
<b>Therapy Area</b>	Oncology/Anti-Infectives

<b>Proposed Solution</b>	<p>The Oncology Division at FDA is now holding workshops and ODAC hearings on endpoints in cancer therapy, with the intent of moving away from survival as this endpoint becomes more confounded by subsequent therapies given to patients upon progression. This is particularly relevant in terms of registering new therapies for treating localized disease.</p> <p>Application of new methodologies should not only focus on new and innovative testing, such as genomics, imaging, bio-informatics, etc., but should expand focus on core skills now in use, like biostatistics, to provide us with approaches to conduct clinical trials more effectively</p>
<b>Timeframe (years)</b>	3-5
<b>Roles</b>	Agency lead, with contributions from NIH and industry.
<b>Comments</b>	

### CMC Aspects of Pharmaceutical Development

Included in the table below are some specific suggestions for improving the efficiency of the CMC 'critical path' aspects of pharmaceutical development:

<b>Hurdle</b>	Establishment of NDA CMC Regulatory Specifications based upon Limited Production Scale Data.
<b>Rank</b>	2
<b>Application (drugs, biologics, ?)</b>	All
<b>Therapy Area</b>	N/A
<b>Proposed Solution</b>	<p>The solution requires a change to the current NDA CMC regulations. Rather than requiring the submission of formal CMC regulatory specifications with each NDA, the NDA CMC regulations should be amended to allow NDAs to contain "interim regulatory specifications" that are based on sound science and product development experience but not so rigid as to preclude changes as additional production scale batches are manufactured and process capability is fully defined. The regulations should allow new pharmaceutical products to be manufactured and tested under "interim specifications" until some future time point, possibly one year post-NDA approval, when formal regulatory specifications would have to be set and finalized by the sponsor. This interim period would allow for additional data collection at production scale so that appropriate specifications could be established based upon actual production experience.</p>

	Importantly, this change would also reduce the number of CMC supplements submitted for FDA review within the first year post-NDA approval.
<b>Timeframe (years)</b>	Less Than 24 Months This proposed solution could be done very quickly and would not require a change to the current NDA CMC regulations.
<b>Roles</b>	Industry must continue to own the role of developing robust products and establishing scientifically sound regulatory specifications. However, the paradigm must shift and allow final regulatory specification setting to occur over a period of time as production-scale experience is obtained by the sponsor and the manufacturing sites. FDA must continue to own the role of modifying existing regulations that have proven to be difficult to meet due to limited product development data and experience at the time of NDA filing. FDA should take the lead in modifying the NDA CMC regulations to allow for the concept of "interim specifications" at the time of NDA filing and approval.
<b>Comments</b>	Due to the nature of the drug development process, most NDAs contain limited data on production-scale batches for both the active pharmaceutical ingredient and the finished dosage form. While technology transfer is sometimes done prior to NDA filing, most transfer work to production scale continues subsequent to NDA filing.  At the time of NDA approval, some additional product-scale data may be available but full production-scale process capability is typically not fully characterized. The establishment of regulatory specifications based on limited pilot or production-scale batches have caused the industry to be saddled with regulatory specifications that are not related to long term production process capability which, in turn, has led to batch rejections and post-approval supplements to change specifications that were set prematurely based on limited product development data and limited production scale experience.