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

**RE: CRITICAL PATH INITIATIVE (DOCKET NO. 2004-N-0181), CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS**

Genentech, Inc. appreciates the opportunity to comment on the Food and Drug Administration's (FDA) report, entitled "Innovation or Stagnation: Challenges and Opportunities on the Critical Path to New Medical Products." As you are aware, Genentech is a leading biotechnology company headquartered in South San Francisco, California. In the 28 years since our founding, we have invested over \$6.4 billion in research and development, and have discovered and introduced 13 significant therapies for serious and life-threatening diseases, including cancer and heart disease. Our record demonstrates that we have been in the forefront of scientific and technical developments, resulting in innovative, safe and effective products using cutting-edge biotechnology processes. We have many more breakthrough products in development at Genentech, highlighting the importance of a renewed FDA commitment to improving drug development processes through the Critical Path initiative.

We agree with the FDA that significant change is needed in order to realize the FDA's stated goal of making drug development faster, more predictable, and less costly. Streamlining the development and approval processes for drugs and biologics provides the greatest and most meaningful opportunity to reduce the overall costs of bringing drugs to market especially for patients with unmet medical needs. To realize this goal, the FDA is also correct that new tools should be created and adopted to improve drug development and review. We appreciate the FDA's recognition of the need for a serious assessment and discussion of existing barriers

Genentech, Inc.  
1 Response to Critical Path Initiative

2004N-0181

JUL2004 C38

and possible solutions to an increasingly costly and slowing drug development process. Only by engaging in active discussion with all of the stakeholders can the FDA render a fair assessment for what can and should be done to improve upon the existing system.

Genentech looks forward to working with the Agency in search of viable methods for accomplishing the goals outlined in the Critical Path initiative, and we suggest several new tools that could help to achieve these goals. Importantly, in looking for new and better ways to develop, evaluate and manufacture therapies, Genentech believes it is equally critical that the FDA evaluate existing review processes and requirements, and consider sensible modifications that would reduce current regulatory burdens. Only then will it be possible for novel ideas developed as a result of the Critical Path initiative to have the intended effect of making drug development faster, more predictable and less costly. This view is broadly shared by other industry leaders and has been communicated to the FDA at multiple public venues.

Specifically, we are concerned that that the FDA's Critical Path document minimizes the FDA's role in creating an environment in which drug development remains too slow, unpredictable, and expensive. The FDA needs to recognize that drug and biologic development has slowed largely because of the unrelenting increase in FDA review and approval standards. For example, the FDA issues dozens of guidances a year, yet each new guidance raises approval standards rather than streamlines or improves upon them. The FDA spends little, if any, time systematically eliminating requirements that are redundant or no longer necessary and that could substantially and positively impact the drug development process.

While we agree that innovation is the key to a more rational and affordable drug development process, innovation without the FDA's acceptance is categorically not useful. Our perception is that even if industry or academia creates new tools, it is unlikely, given the FDA's past practices; the FDA will adopt the new tools or will adopt them uniformly across all review divisions. Furthermore, true innovation should provide justification for the FDA to move away from standards and practices that are outdated or have been proven unnecessary over time. If not, then the

adoption of innovative approaches does nothing to advance the goals of streamlining development. Rather, it has the opposite effect of adding more layers, expectations, requirements and burdens that add to the growing cost and lengthening time of drug development and review.

For the Critical Path initiative to be successful and meaningful, the FDA must demonstrate to industry, through its concerted efforts to drive change and consistency within and across the Center for Drug Evaluation and Research, the Center for Biologic Evaluation and Research, and the Center for Devices and Radiological Health that responsible innovation will be received and embraced, and that outdated regulatory burdens will be removed before new requirements are added.

We view the Critical Path initiative as an event establishing a historical precedent, founded on responsible and thoughtful commitment to the public. We remain optimistic that it will provide a unique and meaningful opportunity to engage in constructive dialogue with the FDA over what works, what doesn't work, where we've been as an industry and as regulators, and where we need to go in the future to fulfill the mission of discovering and developing innovative therapies for patients. With that in mind, we offer the following comments for the FDA's review and consideration. We have divided the hurdles into four areas: those affecting safety; effectiveness; chemistry, manufacturing, and controls; and regulatory. Within each area, we provide an overview and then identify the hurdles. For each hurdle we answer all seven of the FDA's questions. In this manner, each hurdle is considered to be a self-contained section.

### **GETTING TO THE RIGHT SAFETY STANDARDS**

The greatest expense of drug development is driven by the size of clinical trials. Enrollment of a single subject can cost in excess of \$50,000. If fewer subjects were required, product development would be significantly cheaper and faster, since patient enrollment is usually a rate-limiting step in product development. Genentech encourages the FDA to require fewer subjects to be enrolled in clinical trials, which could be achieved by applying risk-based analyses to determine the size of the safety database.

A smaller, yet significant contribution to the cost and inefficiency of product development is when the agency requires a complete battery of toxicology tests for second-generation molecules.

It is important for the FDA to be clear that any product approval and any product administration by a physician to a patient involves risk, and to acknowledge the risks that are inherent in product development. In some cases, we believe it would be appropriate for the FDA to accept more risk by approving products based on less safety data. Thus, we believe that the FDA should inform Congress, patient groups, physicians, public interest groups, and the public generally about what the agency is doing and whether or why it is willing to take more risk in order to get more products onto the market quickly. The FDA should reinforce the message that no drug, biologic, or medical device is safe in any absolute sense, but rather it is a product that may be useful to some patients and that the FDA's initial approval determination is that the risks of the product are outweighed by its benefits, at least in the patient population studied. The FDA should make it clear that an approval does not mean a product is appropriate for every patient, but rather that a critical assessment must be made by the physician and patient before any therapy is used. Physicians and patients need to be reminded of the highly important role they play in making a choice, always based on imperfect information, as to whether a particular product is appropriate under the circumstances.

#### **SAFETY HURDLE NUMBER ONE: SIZE OF SAFETY DATABASE**

1. Hurdle identification: There are several steps the FDA can take to minimize subject exposure. Applying a risk-benefit standard, FDA may tolerate less safety when there is greater effectiveness. Therefore, during a product's development, FDA should balance the degree of safety data requirements with the magnitude of the effectiveness benefit expected. When a patient population has been "enriched" through the use of a diagnostic tool so that the patient population has a higher probability of achieving benefit, then the safety database could be smaller while the agency would still be able to determine whether the product's benefits outweigh its risks.
2. Priority order: Applying a risk-benefit standard when deciding the size of the safety database creates the greatest opportunity for benefit in the safety area.

3. **Product classification:** Applying a risk–benefit standard when deciding the size of the safety database would affect all drugs, biologics, and medical devices for which a diagnostic tool is available.
4. **Disease categories:** no specific disease category.
5. **Nature of solution:** In our “effectiveness” section, we describe efforts that need to be made to spur the development of diagnostic markers. For the safety analysis, the key consideration is convincing the FDA to be “early adopters” of diagnostic markers for the determination of the safety database requirements.
6. **Timeframe:** There are some scientifically legitimate diagnostic markers already used in the scientific community. The FDA should publish the diagnostic markers that may be used to enrich study design and to make certain that all of its review divisions know how to apply diagnostic markers to increase the probability of effectiveness and, thereby, limit the safety database requirements. The FDA could issue a guidance in less than 24 months that gives guidance to both its reviewers and industry on safety database requirements based on enriched designs.
7. **Responsibilities:** The FDA, Pharmaceutical Research and Manufacturers of America (PhRMA), Preclinical Safety Committee (DruSafe), and the Pharmacogenetics Working Group (PWG) are working together. The FDA has held two workshops on pharmacogenetics/pharmacogenomics in drug development and regulatory decision-making. The FDA can work together with these groups and the medical community in determining the criteria for useful diagnostic markers that could be used to enrich studies. Because the creation of new diagnostic markers will be ongoing, the FDA should focus on how to accept and use the markers, not on developing the markers.

#### **SAFETY HURDLE NUMBER TWO: DETERMINE SAFETY DATABASE REQUIREMENTS BASED ON PROPOSED LABEL INDICATION**

1. **Hurdle identification:** The FDA improperly expands the requirements for safety databases by defining database requirements based on potential off-label use. There is an asymmetry between the standards that the FDA applies to companies and the standards it applies to itself. The FDA would never let a company make a claim for a use not studied in a clinical trial. Yet some divisions of the FDA require companies to base the size of their safety databases not on the studied use, but rather on possible off-labeled uses. FDA divisions should be instructed that they must base the size of the safety database needed on the proposed labeled indication, not on the potential for off-label use. A drug has to be proven safe and effective for its intended use, not for any use a reviewer can imagine. Demanding a safety

package that supports indications not sought by the Sponsor is beyond the FDA's statutory authority and it inappropriately expands drug development times.

2. Priority order: Defining database requirements based on potential on-label (and not off-label) use is our second highest priority in the safety area.
3. Product classification: This hurdle applies to all drugs, biologics, and medical devices.
4. Disease categories: This hurdle applies to several categories of diseases, including Endocrinologic and Metabolic; Pulmonary-Allergy; and Analgesia and Anti-Inflammatory.
5. Nature of solution: A simple directive to the review divisions that the requirements for all safety databases must be based on the indication studied, not on a possible off-label use, would be sufficient.
6. Timeframe: This could be accomplished quickly, in a matter of weeks, depending on the FDA's priorities.
7. Responsibilities: The FDA should make the change and publish it so that both reviewing divisions and industry are aware of the change.

### **SAFETY HURDLE NUMBER THREE: COMPLIANCE WITH ICH GUIDELINES**

1. Hurdle identification: Drug development is unpredictable and unnecessarily expensive because the FDA's divisions routinely ask companies for safety data packages that exceed ICH guidelines. ICH guidelines were based on sound science regarding the likelihood that a sponsor, the FDA, or another regulatory agency would pick up a side effect at a certain frequency. The international regulatory community made a considered judgment that pre-approval drug development data collection efforts could not reasonably find all adverse events, and thereby limited the size of the safety data packages needed for approval. Yet over time the FDA has become far more "risk averse" and is frequently unwilling to accept safety data packages that meet ICH guidelines. Our study of NMEs (for both acute and chronic conditions, excluding blood and vaccines) approved during 1996–2003 indicates that the average size of the safety database is over 2000 subjects.

The FDA has recognized that no clinical trial database will be big enough or have enough chronic treatment data to answer conclusively all potential safety issues. The FDA should limit its safety requests to ICH standards, and if any review division seeks to increase the safety database beyond those standards, the division should be required to bear the burden of explaining what additional information will be obtained and why the delay

and added expense are necessary. The FDA should establish criteria under which expanded safety databases may be asked for, and the FDA should create a cross-center review committee to review and approve division requests for expanded safety databases. If ICH standards are to have meaning, the FDA should not demand data in excess of more than a small percentage (5%–15%) of their application reviews. In addition, if the agency then asks for additional data, it should be required to determine and publish whether the additional data made any significant difference in the product's approvability, so that patients and caregivers can determine whether keeping the product off the market is a net plus or minus from the patients' perspective.

2. Priority order: Limiting safety databases to ICH standards is our third priority in the safety area.
3. Product classification: Limiting safety databases to ICH standards applies to all drugs and biologics.
4. Disease categories: Limiting safety databases to ICH standards applies to all chronic diseases.
5. Nature of solution: A simple directive to the review divisions that all divisions may not require safety databases in excess of ICH standards without upper management and peer review would be the first step. Convening a group of seasoned, senior managers to grant waivers and to monitor review division compliance would be an important related step. The FDA should also consider giving a directive, based on the Agency's accumulated knowledge and data, to reviewing divisions on how often it would expect to see a waiver request, e.g., in 5%–10% of all clinical trials.
6. Timeframe: This could be accomplished quickly, in a matter of weeks, depending on the FDA's priorities.
7. Responsibilities: The FDA should notify immediately all review divisions that they may not require safety databases in excess of ICH standards without prior approval. It should then publish its position so that both reviewing divisions and industry are aware of the change. The FDA should then convene a small, senior task group to monitor requests for deviation, and that group should track which divisions are asking for waivers and whether the justifications offered have merit. When additional safety data are requested, the FDA should review the additional data that were in excess of the ICH requirement and determine whether the data provided significant additional safety information.

## **SAFETY HURDLE NUMBER FOUR: SAFETY DATA IN REQUIREMENTS IN SUBGROUPS**

1. Hurdle identification: The FDA, as an institution, knows that no matter how large the safety database is prior to approval, that there will still be new information identified after the product is on the market and is then used by many times more persons in less-controlled settings. However, the FDA appears uncomfortable with this fact; the size of safety databases remain very large in order to “know everything” about all patient subpopulations before a drug is put on the market and used by any subpopulation. Again, our analysis of approvals during 1996–2003 indicates that since FDA started its “risk management” efforts, the number of post-marketing commitments has increased significantly.

There is no doubt that drug development is longer and more expensive due, in part, to the ever-increasing list of studies that FDA requests industry to conduct. The agency now routinely requires multiple drug-drug interaction studies and studies in several subpopulations; the elderly, children, persons with hepatic impairment, persons with renal impairment, etc. before a drug or biologic is made available commercially to any patients. FDA reviewers also ask for safety data for increasingly smaller subpopulations, e.g., a study in asthmatics who also smoke. This caution drives the need for more and more trials with more and more subjects prior to approval. Yet all will never be known about every patient subset before approval, if for no other reason than the subsets that can be studied are infinite.

The FDA needs to limit its requests for data to information that is needed for a determination of whether the product should be put on the market, but should not attempt to define the precise limits of safety in every subpopulation before approval. The FDA should reorder its priorities and recognize that its first priority is to let a product with an acceptable overall risk-benefit profile onto the market and permit the precise contours of the product’s safety and effectiveness in subpopulations to be studied post-approval. Patients and their providers should be made aware that a given subpopulation may never be studied, so that false hope is not offered. However, the FDA must also let competent physicians and patients have a choice as to whether they are willing to take a product for which safety overall, but not the safety for their patient subset has been ascertained. The FDA should also strive to work with academia and sponsors to find animal models that would permit studies in animals to be substituted for the various subpopulation trials that are currently required.

2. Priority order: Initial approval of products without safety data in all subsets of potential patients is our fourth priority in the safety area.

3. Product classification: Approving products without safety data in all subsets of potential patients applies to all drugs, biologics, and medical devices.
4. Disease categories: Approving products without safety data in all subsets of potential patients applies to all diseases.
5. Nature of solution: A simple directive to the review divisions that they should not wait for all subset data before approval would be an important first step. The FDA should publish that information so that both industry and FDA reviewers would know of the new standard.
6. Timeframe: This could be accomplished quickly, in a matter of weeks, depending on the FDA's priorities.
7. Responsibilities: The FDA could play the pivotal role in informing entities of its new approach. Others, such as academia, could monitor the situation to determine whether significant problems have occurred using smaller safety databases.

#### **SAFETY HURDLE NUMBER FIVE: NONCLINICAL REQUIREMENTS FOR SECOND GENERATION MOLECULES**

1. Hurdle identification: The nonclinical requirements for a second-generation molecule often require the innovator with the product development history, and experience with the protein product's attributes and characteristics repeating the toxicology studies it performed for the parent molecule for the second-generation molecule. An innovator repeating all of the toxicology studies is very costly, frequently redundant and an unnecessary use of animals; especially if differences between the parent molecule and the second-generation molecule are unlikely to have different toxicological effects.
2. Priority order: Applying fewer toxicology requirements to second-generation products is our fifth priority in the safety area.
3. Product classification: Applying fewer toxicology requirements to second-generation products would be applicable to recombinant protein products regulated as drugs or biologics.
4. Disease categories: Applying fewer toxicology requirements to second-generation products applies to all diseases.
5. Nature of solution: A simple directive to the review divisions that they should consider requiring less toxicology data on second-generation products would be an important first step. The FDA should publish the information so that both industry and FDA reviewers would know of the new standard. The FDA could then work with other groups, e.g., Biotechnology

Industry Organization (BIO), Pharmaceutical Research Manufacturers Association (PhRMA), the Preclinical Safety Committee (DruSafe), and others to develop more explicit standards for what could be required under various circumstances. That information could be handled through the FDA's Good Guidance Practice standards.

6. **Timeframe:** The directive could be accomplished in a few months. Developing a new guidance document would take longer, but certainly less than 24 months.
7. **Responsibilities:** Given the constraints on the FDA's resources, much of the planning and running of a workshop on this issue could be handled by industry groups, with FDA participation at the workshop. The FDA's principal role would be to decide on which toxicology tests could be eliminated for an innovator's second-generation products and to disseminate that information to its review divisions and industry.

#### **SAFETY HURDLE NUMBER SIX: ELIMINATION OF REDUNDANT OR OUTDATED TESTING AND REGULATORY REQUIREMENTS**

1. **Hurdle identification:** When the FDA adopts a new analytical method, it should publish the requirement so all companies and, perhaps more importantly, all review divisions are aware of the new standard. For example, not all review divisions permit reliance on the transgenic mouse model (in lieu of two-year animal carcinogenicity trials) that the FDA helped to develop and highlights in the Critical Path report. More generally, as the FDA substitutes more modern tests for outdated methods, it should provide a running list of requirements/tests that have been eliminated.
2. **Priority order:** The FDA providing a running list of all requirements/tests that have been eliminated is our sixth priority in the safety area.
3. **Product classification:** The FDA providing a running list of all requirements/tests that have been eliminated applies to all drugs, biologics, and medical devices.
4. **Disease categories:** The FDA providing a running list of all requirements/tests that have been eliminated applies to all diseases.
5. **Nature of solution:** A simple directive to all review divisions that they should use new analytical tools as they become available, coupled with a list of new methods suitable for use and old tests that have been abandoned, would be sufficient.
6. **Timeframe:** The development of a template for advising reviewing divisions of what new methods they should accept and what old tests have been abandoned could be done quickly. A few examples would be sufficient for a

first iteration. Thereafter, the list could be updated as FDA reviewers started to accept new analytical tools and inform senior management they are accepting the tests, so that the new methods could be added to the list. Similarly, the “abandoned test” list could grow as reviewers remember what old tests they are no longer requiring or as senior management directs reviewers to abandon old, scientifically obsolete tests.

7. Responsibilities: The FDA should provide consistent information to the review divisions and industry and it should manage the review divisions so they follow the direction as to which tests should be used and which tests are rejected as obsolete. The NIH or industry could convene a workshop to evaluate evidence and suggestions on which tests should be abandoned or substituted.

### **GETTING TO THE RIGHT EFFECTIVENESS STANDARDS**

The need to get therapies approved quickly will always lead to the question of whether more could have been done prior to approval; whether more scrutiny of the application might have uncovered other safety issues or risks or could have provided a better understanding of how to use the product. We believe that the agency has a responsibility to ensure that all FDA resources are utilized to provide the maximum benefit to patients. Requests for information or allocation of resources to review information that is not essential to evaluating the safety and effectiveness of a product is inefficient and costly, and is an area where meaningful improvement is possible. Our highest effectiveness priority is for the FDA to ensure that reviewers are only requesting information that is essential to determine the effectiveness of a product to treat the intended indication. The agency can achieve this by applying risk-based analyses to determine how much evidence is required to support approval to treat the intended patient population.

The ability to develop medications that treat disease and improve quality of life has spurred greater demand from health care consumers for still more life-improving and extending treatments. As the U.S. population continues to expand and age, the demand for new and better products will only increase. However, continuing to identify and develop superior therapies is becoming progressively more difficult. Consequently, establishing the requirements for demonstrating evidence of effectiveness that are logical and meaningful is becoming increasingly more critical.

## **EFFECTIVENESS HURDLE NUMBER 1: LACK OF PRESCRIBING INFORMATION FOR SCIENTIFICALLY ESTABLISHED USES**

1. Hurdle identification: Many newer uses of approved products for severe and life-threatening diseases, specifically for the treatment of cancer and autoimmune diseases, are common in clinical practice. These new uses are frequently not listed in product labeling despite the fact that they are supported by published data from clinical studies. If the information in the scientific literature is adequate for the medical community to determine the most appropriate treatments, this information should also be adequate to support efficacy-labeling supplements.

The FDA's Guidance for Industry, *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products*, issued in December 1998 is an example of the absence of a standard for labeling revisions for scientifically established uses. The guidance clearly defines the standards for updating labeling information for new uses for approved products. However, the guidance has not improved the agency's process for approving supplemental applications for scientifically established uses.

The requirement for concurrently controlled randomized studies with clinical endpoints (e.g., survival and/or symptomatic benefit) for therapies that have become widespread in the treatment of severe and life-threatening diseases does not facilitate the addition of safe and effectiveness information to drug labeling. In addition, the majority of patients with severe and life-threatening diseases are not willing to enroll in randomized studies evaluating established treatments if there is a possibility they will receive a placebo or an inferior treatment.

2. Priority order: The lack of prescribing information for scientifically established uses is limiting and delays the use of the most effective therapies; the lack of information also can result in the use of inappropriate dosing and administration schedules. Developing standards to facilitate updating prescribing information to reflect current clinical practices creates the greatest opportunity for demonstrating medical utility. This will ensure that the medical community will have access to all the data establishing the product's safety and effectiveness.
3. Product classification: Updating the prescribing information to reflect established uses applies to all drugs, biologics, and medical devices.
4. Disease categories: Updating the prescribing information to reflect established uses to apply to several categories of diseases, especially severe and life-threatening diseases.

5. Nature of solution: The FDA needs to minimize the barriers for updating labeling to reflect established treatments for severe and life-threatening diseases. The requirements for clinical data needed to support a supplemental application to add a scientifically established use to the prescribing information should not be the same as the requirements for the data needed to support the addition of a new use of an approved product. Evidence of safety and effectiveness extrapolated entirely from published studies, or data from nonrandomized studies demonstrating a treatment provides a benefit with tolerable treatment toxicity should be adequate to support supplemental applications for all commonly used drugs and biologics for the treatment of severe and life-threatening diseases.
6. Timeframe: Revising the 1998 Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, and the FDA Guidance for Industry, *FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products*, to delineate between the requirements for data supporting supplemental applications for a new use and a scientifically established use could be accomplished very quickly.
7. Responsibilities: The FDA should revise the aforementioned guidances, distribute the revised guidances for comment, and publish the final documents so that both reviewing divisions and industry are aware of the changes.

## **EFFECTIVENESS HURDLE NUMBER 2: USE OF PHARMACOGENOMIC DATA AND VALIDATION OF BIOMARKERS**

1. Hurdle identification: We applaud FDA for its willingness to work with industry to develop the draft guidance on Pharmacogenomic Data Submissions. Use of biomarkers holds great promise to shed scientific light on predicting which individuals have a greater chance of benefit or risk, thus, helping to maximize the effectiveness and safety of drugs.

The use of biomarkers to guide therapy will constitute a significant shift from the current practice of population-based treatment toward "fine-tuning" individual therapy. However, it is essential that the availability of promising new therapies not be slowed because of delays caused by the performance of additional studies validating the biomarker.

Currently, we do not have adequate nonclinical tools to identify a patient-selection biomarker in time to incorporate it into the design of a pivotal trial. Consequently, it is frequently not possible to prospectively predetermine a biomarker for enhancing dose selection, safety, or effectiveness of a drug. The inclusion and exclusion criteria in a pivotal trial

cannot be based on genotype or gene expression profile. However, retrospective analysis of pivotal trial data may highlight a specific probable valid biomarker<sup>1</sup> for subpopulations with enhanced response to therapy. Performing a second study to generate additional clinical data to validate the biomarker will increase the costs of new therapies and unnecessarily delay the availability of new drugs and biologics for the treatment of severe or life-threatening diseases.

2. **Priority order:** Development of the FDA's planned guidance on the Co-Development of Pharmacogenomics and Drugs addressing the standard of accepting postapproval studies to validate the biomarkers is our second priority for demonstrating medical utility. This will ensure that the development path is as efficient as possible.
3. **Product classification:** Defining validation requirements for biomarkers applies to drugs and biologics.
4. **Disease categories:** Defining validation requirements for biomarkers applies to all disease categories.
5. **Nature of solution:** We suggest the degree of evidence required to support the use of biomarker data to be considered sufficiently reliable to serve as the basis for a regulatory decision should be based on several factors, including the following: (1) the indication and the claim; (2) internally consistent, multicenter study; (3) the knowledge of the interaction of the disease and condition and the product. In certain circumstances, in particular for severe and life-threatening diseases, it may not be appropriate to require independent substantiation of a biomarker from another controlled trial to support approval. Postapproval studies may be the most appropriate and least burdensome means to validate the biomarker.
6. **Timeframe:** Biomarker validation standards could be implemented in less than 24 months. The process for developing standards and guidances is already in progress.
7. **Responsibilities:** The FDA, PhRMA, DruSafe, and the Pharmacogenetics Working Group (PWG) are working together. The FDA has held two workshops on pharmacogenetics/pharmacogenomics in drug development and regulatory decision-making.

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<sup>1</sup> Data sufficient to establish a significant association between a pharmacogenomic test result and clinical outcomes.

### **EFFECTIVENESS HURDLE NUMBER 3: NEW STATISTICAL APPROACHES TO CLINICAL TRIALS**

1. Hurdle identification: There is resistance to consider alternative analysis and design methodologies that could improve efficiency of drug development. There is no incentive for sponsors to explore alternative (but appropriate) methods. The default is to always use what others have done in the past.

For example, the use of repeated measures analysis can provide valid inferences and better handling of missing data than more conventional methods. Also, FDA often requires that the primary efficacy endpoint be a categorization of an essentially continuous endpoint; such categorization discards information, resulting in larger trials. Finally, there is no common FDA position on what evidence is required from clinical trials to support the inclusion of results on secondary endpoints into product labeling. Such endpoints often provide useful information for patients and prescribing physicians.

2. Priority order: Evaluating alternative methods and identifying acceptable alternative options is our third priority for demonstrating medical utility.
3. Product classification: Evaluating alternative statistical analysis methods and identifying acceptable alternative options applies to drugs, biologics, and medical devices.
4. Disease categories: Evaluating alternative statistical analysis and identifying acceptable alternative options applies to all diseases.
5. Nature of solution: Create a formal forum between FDA, industry and academic statisticians and clinicians with a goal of evaluating alternative methods for common issues and providing the FDA and industry with a set of acceptable options.
6. Timeframe: A workshop could be convened within the next 12 months.
7. Responsibilities: A workshop convened by NIH or industry to evaluate evidence and suggestions on which methodologies should be abandoned or substituted will be the most effective forum for developing standards.

### **EFFECTIVENESS HURDLE NUMBER 4: IDENTIFYING THE APPROPRIATE CONTROL ARM TO SUPPORT AN EFFECTIVENESS DETERMINATION**

1. Hurdle identification: According to existing regulations, a new drug or a biologic may be approved based on adequate and well-controlled trials establishing the product provides a meaningful therapeutic benefit over existing therapies (see 21 CFR 314.126). In addition to patients who do not

benefit from or cannot tolerate available therapy, there are several diseases without an approved standard of care or that have an outdated standard of care that the medical community has abandoned in favor of an unapproved therapy. Therefore, choosing a treatment for the control arm for studies in these patient populations is problematic. This issue is particularly problematic for clinical investigations in patients with diseases for which a placebo-only controlled trial is difficult to conduct based on ethical grounds, or when the medical community has adopted the use of an unapproved therapy that it believes is more effective than the approved treatments. In addition, determining the appropriate size to power the study is problematic because of the lack of guidance on the level of effectiveness that is needed to demonstrate a clinical benefit. We recognize that FDA's recent Guidance for Industry, Available Therapy, touches on this topic, but it still leaves the standards quite vague, especially in oncology.

2. Priority order: Articulating how the agency currently views the use of inadequate therapies as controls will enable sponsors to design drug development programs sufficient to establish effectiveness without being excessive in scope. This is our fourth priority for demonstrating medical utility.
3. Product classification: Identifying the appropriate control arm to support an effectiveness determination applies to drugs, biologics, and medical devices.
4. Disease categories: Identifying the appropriate control arm to support an effectiveness determination applies to diseases that do not currently have adequate treatment options or that have outdated approved treatments, and do not qualify for accelerated approval.
5. Nature of solution: The FDA, industry, and academia need to identify the quantitative standards for demonstrating effectiveness of drugs and biologics for the treatment of diseases that do not currently have adequate treatment options and do not qualify for accelerated approval. The FDA also needs to clarify whether it will accept the European unapproved but commonly used therapy as an appropriate control arm for diseases without an approved standard of care.
6. Timeframe: The agency has already started to work on developing standards for trial designs for non-life-threatening diseases, e.g., the Systemic Lupus Erythematosus Draft Concept paper, the Arthritis Advisory Committee meeting held on 29 and 30 September 2003. Development of guidances for each disease with inadequate therapies is an extensive project and will require a long-term prioritization plan. Since the timeframe is long, an annual, publicly held meeting to update and inform sponsors, the

medical community, and patients of any changes or developments would be informative and helpful.

7. Responsibilities: A workshop convened by FDA with the medical community to discuss and identify incorporation of the most appropriate control arms into clinical trial designs will be the most effective forum for developing standards. Simultaneous and independent development of guidances for several diseases that is led by academia and the medical community will ensure that guidances and standards are developed as quickly as possible.

### **TOOLS FOR GETTING TO THE RIGHT MANUFACTURING STANDARDS**

Problems with scale-up and mass production of biotechnology products can slow development and escalate costs. With years of experience in development and production (both successful and failed), many well-established biotechnology companies possess the knowledge on issues (e.g., critical control parameters, essential tests for product release and for monitoring product stability) critical to producing a therapeutic product with consistent high quality and to maintaining the quality throughout the product's shelf life. The Agency has been overtly discounting the value of this vast technical experience base. Currently, the FDA is involved in an extensive, multi-year effort to incorporate the most up-to-date science into its regulation (i.e., review and inspection process) of pharmaceutical manufacturing and to encourage industry to adopt innovative manufacturing technologies. It has also become apparent to us that the amount of facility and GMP-related information required for a Biological Licensing Application (BLA) has been steadily increasing over the past few years. This practice clearly goes against the spirit of one REGO (Reinventing Government) initiative, i.e., minimizing the submission of facility and GMP-related information to BLAs.

Manufacturers are increasingly facing numerous regulatory hurdles that hinder the advancement of science and technology. These hurdles have resulted in a significant waste of resources and time, without a noticeable improvement in product quality or benefit to patients. Eliminating such waste will free up resources urgently needed for developing novel therapeutic products and new therapies.

## **MANUFACTURING HURDLE NUMBER 1: LACK OF PRIORITY SETTING IN REVIEW (PARTICULARLY FACILITY AND GMP RELATED) AND INSPECTION**

1. Hurdle identification: It appears that recently, the focus of the review has drifted from scientific issues to enforcement issues. All manufacturing and control issues are treated with equal weight or emphasis, and are not evaluated based on their relative risk or scientific significance to product quality or the product's intended use. The only available risk-based tools are the regulation and guidance for post-approval changes. However, the regulation and guidance not only are inadequate and outdated in many areas, but they also are often interpreted inconsistently by FDA personnel. Risk-based tools guiding pre-approval reviews and inspections of biotechnology products simply do not exist. We recognize that under ICH, a guidance covering the Pharmaceutical Development (Section 3.2.P.2 of the Quality Module of the Common Technical Document) is under consideration. The admirable goal of this project is that information contained in Section 3.2.P.2 could be used by FDA reviewers for risk assessment. However, we do not believe that this project will result in a relief of current excessive regulatory burdens with respect to validations of equipment and process and facility inspections. Another project being considered by ICH is developing a guidance on Risk Management: Application to Quality Requirements and Practices. This high level document may be useful to establish a conceptual framework. The final relief of regulatory burden lies in the interpretation and implementation of the concepts established.

The FDA should focus resources on top-priority issues, providing the greatest benefit to patients. Manufacturing experience and compliance history should be used when assessing the frequency and scope of inspections. The FDA should define the standards and expectations for pre-approval inspections. It should also apply a matrix approach for inspections based on the similarity of molecular structure and manufacturing process (e.g., the same class of antibodies produced by Chinese hamster ovary cells). Also, a family approach for manufacturing and facility changes should be instituted to eliminate redundant validation and qualification requirements for multiple pieces of identical equipment.

2. Priority order: Focusing the FDA's resources on top-priority issues providing the greatest benefit to patients is our number one priority in the manufacturing area.
3. Product classification: Focusing the FDA's resources on top-priority issues providing the greatest benefit to patients applies to all drugs, biologics, and medical devices.

4. Disease categories: All diseases categories are affected because biotechnology products are approved/ licensed or are being studied for treating a variety of diseases.
5. Nature of solution: The FDA could issue interim internal inspection and review guides and policies and guidances for industry to address those simple, clear cut solutions to the problems as suggested above without waiting for the finalization of the two new ICH guidances.
6. Timeframe: Internal inspection and review guides and policies, and guidances for industry could be issued in less than 24 months.
7. Responsibilities: The FDA should work with industry to formulate new approaches.

**MANUFACTURING HURDLE NUMBER 2: LACK OF CONSISTENCY IN REVIEW OF INFORMATION (PARTICULARLY FACILITY AND GMP RELATED) SUBMITTED TO ORIGINAL BLAS OR SUPPLEMENTS, AND IN THE INSPECTION OF MANUFACTURING SITES**

1. Hurdle identification: Educational background and work experience vary widely among FDA facility reviewers and inspectors (investigators), leading to inconsistent requirements for similar processes or similar products within the same company. The FDA should ensure that its personnel have the skills and expertise needed to review and inspect innovative manufacturing and testing technologies. To achieve this goal, the FDA should establish an effective in-house training program and an industry-residence program and FDA should recruit review/inspection staff with adequate science backgrounds and pharmaceutical manufacturing experience.
2. Priority order: Ensuring that FDA personnel have the relevant skills and expertise to review and inspect innovative manufacturing and testing technologies is our second priority.
3. Product classification: Ensuring that FDA personnel have the relevant skills and expertise applies to all drugs, biologics, and medical devices.
4. Disease categories: Ensuring that FDA personnel have the relevant skills and expertise applies to all diseases.
5. Nature of solution: An FDA in-house training program, an industry-residence program and recruitment of review/inspection staff with adequate science background and pharmaceutical manufacturing experience should be considered.

6. Timeframe: This is a long-term project, but the FDA could significantly improve the skills and expertise of its personnel in 24 months through effective training and targeted recruitment.
7. Responsibilities: The responsibility of improving the skills and expertise of its personnel lies mainly with FDA. However, Genentech is willing to host a residence program for FDA personnel.

### **MANUFACTURING HURDLE NUMBER 3: LACK OF A RISK-BASED ANALYSIS AND A SCIENCE-BASED APPROACH IN DERIVING THE REQUIREMENTS FOR VALIDATION STUDIES ON EQUIPMENT AND PROCESSES**

1. Hurdle identification: Often redundant or irrelevant work must be performed by companies. The FDA should focus validation requirements on a risk-based analysis (critical process parameters) and a science-based approach. FDA should encourage the acceptability of a validation program in lieu of ongoing testing. FDA should determine the degree of validation and testing that is required to support process improvement based on manufacturing and compliance history.
2. Priority order: Focusing validation requirements based on a risk-based analysis (critical process parameters) and a science-based approach is our third priority.
3. Product classification: Focusing validation requirements applies to all drugs, biologics, and medical devices.
4. Disease categories: Focusing validation requirements apply to all diseases.
5. Nature of solution: The FDA could issue internal inspection and review guides/policies, and guidances for industry to establish new approaches.
6. Timeframe: Establishing risk- and science-based validation requirements for equipment and processes could be done in less than 24 months.
7. Responsibilities: The FDA should work with industry to establish validation requirements for equipment and processes.

### **MANUFACTURING HURDLE NUMBER 4: LACK OF RECOGNITION OF MANUFACTURING AND TESTING EXPERIENCE AND DATA ACCUMULATED OVER TIME IN THE POST-MARKETING SETTING**

1. Hurdle identification: Revising process control and product specifications post-approval has been difficult. Standards for product specifications based on manufacturing experience post-approval should be defined. It is important to assess testing requirements based on experience and FDA should to eliminate redundant testing as identified by manufacturing and

testing experience. The FDA should adopt the same approaches (e.g., skip lot testing, sunset of certain tests post-approval) that are already in place for chemical drugs.

2. Priority order: The FDA's recognition of manufacturing and testing experience and data accumulated over time in the post-marketing setting is our fourth priority.
3. Product classification: Modifying in-process and final specifications based on manufacturing experience applies to all drugs, biologics, and medical devices.
4. Disease categories: Modifying in-process and final specifications based on manufacturing experience applies to all diseases.
5. Nature of solution: The FDA could issue guidances to establish new approaches.
6. Timeframe: A workshop co-sponsored by American Association of Pharmaceutical Scientists (AAPS), the FDA, and industry on specifications for biotechnology and biological products is scheduled for October-2004. Standards and testing requirements based on manufacturing and testing experience and data could be established and implemented soon after.
7. Responsibilities: The FDA should work with industry to establish standards and testing requirements.

### **GETTING TO THE RIGHT REGULATORY STANDARDS**

Genentech believes that there are four crucial scientific and technical dimensions on the path from scientific innovation to commercial product. Applying appropriate review standards to applications is equally as important as the other three dimensions outlined in the Critical Path Initiative. The Prescription Drug User Fee Act of 1992 (PDUFA) and the FDA Modernization Act of 1997 (FDAMA) gave the FDA the mandate and resources to create a faster and more efficient review process for new treatments, while FDAMA helped lower obstacles to new drug application approvals. Additional reforms should now be instituted to revamp the FDA's policies and processes to efficiently review the volume of applications submitted for new molecular and chemical entities, in addition to supplements of new uses for approved products.

A more sophisticated designation process to ensure the speed, quality, and scrutiny of reviews is appropriate. The FDA needs to accept and apply the benefits of

modern statistical methods to promote more product development programs and approvals.

### **REGULATORY HURDLE NUMBER 1: MINIMIZE REDUNDANCIES IN DEVELOPMENT PROGRAMS SUPPORTING WORLDWIDE APPROVALS**

1. Hurdle identification: A key to obtaining timely approval of a New Drug or License Application is the early development of an overall regulatory strategy. To ensure that a plan is acceptable to multiple health authorities, a Sponsor has to present the development plan and regulatory strategy to several health authorities. There is no formal procedure to obtain simultaneous scientific advice from various health authorities.

The process for obtaining scientific advice from several health authorities is redundant and costly. In addition, the advice is not always consistent, resulting in individualizing portions of the development programs to fulfill the requests from the various health authorities. This situation can be made even more complicated when different countries have differing therapies as the approved standard of care.

2. Priority order: Minimizing the redundancies in development programs supporting worldwide approvals creates an important opportunity that could have broad benefits in accelerating the pace of development while raising scientific standards.
3. Product classification: This hurdle applies to drugs, biologics, and medical devices.
4. Disease categories: Creating a parallel scientific advice program applies to all serious and/or life-threatening diseases.
5. Nature of solution: Convert the current pilot program evaluating the creation of a parallel scientific advice program for the development of important new therapeutic products into a formal procedure; and expand the program to include other health authorities, e.g., Canada, Australia, and Japan.
6. Timeframe: As outlined by the FDA's Acting Deputy Commissioner for International and Special Programs<sup>2</sup>, the pilot program has already been created. The FDA together with other interested health authorities could create a formal program in less than 24 months that gives guidance on request procedures and applicable classes of therapies.
7. Responsibilities: The FDA should convene all interested health authorities.

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<sup>2</sup> June 2004 Drug Information Association Annual meeting.

## **REGULATORY HURDLE NUMBER 2: RISK MANAGEMENT**

1. **Hurdle identification:** The FDA must be willing to take risks and perform a review adequate to assess the benefits and risks of a new product or use. The agency has successfully initiated streamlined reviews of applications with a priority designation. However, there is no application review designation process based on the amount and nature of the evidence of effectiveness or on the safety concerns.

Likewise, there is no process to categorize reviews, based on a sponsor's development, compliance history, and manufacturing experience. Equal resources are assigned to applications with high benefit and low risk and to applications with benefit-risk concerns.

Similarly, the FDA should be willing to accept a risk-management approach to identify areas of concern in the development program and apply appropriate resources to address potential issues, e.g., the FDA's expectation of monitoring 100% of Case Report Forms is inefficient and very costly. The agency needs to be more willing to accept and acknowledge the benefits of modern statistical methods and use these tools to determine appropriate monitoring requirements.

Applying the same review polices to all applications is an inefficient use of resources that can delay the review and approval process.

2. **Priority order:** Applying a risk-benefit analysis to determine the resources necessary to perform reviews is our second regulatory priority.
3. **Product classification:** This hurdle applies to drugs, biologics, and medical devices.
4. **Disease categories:** This hurdle applies to all disease categories.
5. **Nature of solution:** In an era of concerns about the affordability of health care, the FDA needs to ensure that application reviews are as streamlined and efficient as possible. The FDA needs to create a range of application review processes and ensure that each application is reviewed as efficiently as possible to determine a product's safety and effectiveness. It is important that FDA considers the costs of performing additional studies, and to determine if the cost and delay of obtaining additional information will be balanced by the benefit to patients.
6. **Timeframe:** The current review designation process could be expanded within the next 24 months.
7. **Responsibilities:** The FDA should develop standards and publish them so that both reviewing divisions and industry are aware of the new expectations.

Again, Genentech appreciates the opportunity to provide input to the FDA on the Critical Path initiative. Recent challenges faced by the biomedical industry highlight the need for a constructive set of solutions to the increasingly demanding drug development and review processes. Clearly, FDA leadership is needed to effect change within the Agency, as well as within the research industry and among external stakeholders. We continue to support the push for new tools that would make the drug development process more efficient and, therefore, more affordable. However, we emphasize again the importance of removing barriers to make room for new and improved assessment and development tools. Without meaningful reform of current regulatory processes, the FDA's Critical Path initiative will serve only to exacerbate development challenges and costs, not improve upon them.