Carlo Russo, MD
Director
Worldwide Regulatory Affairs
Vaccines/Biologics

Merck & Co., Inc.
P.O. Box 4, UN-B121
West Point PA 19486-0004
Tel 610 397 7610
Fax 610 397 2962
Email: carlo_russo@merck.com

March 9, 2001

MERCK
Research Laboratories

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

Dear Sir or Madam:

RE: [Docket No. 00N-0989]
***Notice: Agency Information Collection Activities: Submission for OMB Review: Comment Request;* Proposed Rules on Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation**

Merck & Co., Inc., is a leading worldwide human health product company. Through a combination of excellent science and state-of-the-art medicine, Merck's R&D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division is one of the leading U.S. biomedical research organizations. MRL tests many compounds or potential drug candidates at one time through comprehensive, state-of-the-art R&D programs that include basic research and discovery, developmental studies in animals, manufacturing quality assurance testing, and, finally, human clinical research.

In the course of bringing product candidates through developmental testing Merck is well versed in all aspects of the design and conduct of clinical trials on a wide range of products. For these reasons, Merck is very interested and well qualified to comment on the Food and Drug Administration's (FDA's) Proposed Rule on Availability for Public Disclosure and Submission to FDA for Public Disclosure of Certain Data and Information Related to Human Gene Therapy or Xenotransplantation, cited above (hereafter referred to as the Proposed Rule). Comments are being provided here to OMB on the information collection requirements of this proposal (under the Paperwork Reduction Act of 1995) and are also submitted to the Dockets Management Branch at FDA. Additional technical comments on the proposed rule will be submitted to the Dockets Management Branch by April 18, 2001.

General Comments (Information Collection Requirements)
The information collection procedures in the Proposed Rule are only reasonable if FDA's central premises underlying the Proposed Rule are correct. These premises are expressed in the intended purpose of this Proposed Regulation, namely prevention of unique problems in clinical trials in these therapy areas. The first premise is that publicly releasing trade secret, commercial or financial information of commercial sponsors of gene therapy trials will have the public health impact of preventing the widely publicized problems of non-commercial sponsors of clinical trials

00N-0989 C10

trials using similar products. The second underlying premise is that this commercial trade secret and confidential information is already publicly available and that there is only "...minimal incremental commercial value associated with the information that may be disclosed [under the Proposed Rule],"

Merck respectfully disagrees with both of these assumptions. Thus, there is no justification or foundation for promulgation of this Proposed Rule. The practical, legal and technical reasons underlying our position are as follow:

1. Release of confidential commercial information will not prevent problems in non-commercial clinical research, nor provide the intended public health or education benefit.

FDA states, but does not provide evidence, that releasing the confidential IND information of commercial sponsors of product applications in this field (–sponsors who are regulated and monitored by FDA -) will prevent problems that have been documented and reported in the non-commercial sector of clinical research, where adherence to FDA regulations has been frequently ignored. Disclosure of information in the gene therapy trial where a widely publicized tragedy occurred would not have been prevented by disclosure of early developmental information. The more fundamental issues of proper supervision of gene therapy trial and adherence to FDA-advised Good Clinical Practice (GCP) reporting of adverse events would more appropriately effect the intended outcome.

It is doubtful that disclosure of commercial information at the time of filing an IND and thereafter prior to licensing application filing will serve any useful purpose other than to prematurely disclose commercial research strategies to competitors at a very critical time in their evolution. Furthermore, it is doubtful that public disclosure of highly technical information would provide educational value.

FDA contends that its Proposed Rule is justified by the positive effect it will have on public health, presumably to expose information for more informed medical decision-making by practitioners and patients. However, practitioners and patients would be involved in use of investigational agents only as part of clinical trials. In this situation, the informed consent document which contains full disclosure of risks and benefits permit study participants to make a determination about the proposed clinical trial. Thus, the informed consent document should accomplish the intended purpose of providing information to practitioners and study participants without imposing disclosure of proprietary information.

2. Trade Secret Information.

FDA explicitly states that "[w]hile trade secret information . . . is present in all INDs and biological product files, including those subject to this proposed rule, this proposal will not affect the confidentiality of such information . . . ." 66 Fed. Reg. 4692-93. This statement seems to be in tension with the language of the Proposed Rule, which requires broad disclosure of information that appears to include trade secret information, such as identification of the biological product and a general description of the method of production, product and patient safety data, including pre-clinical assessment results and feasibility studies (i.e. immunogenicity); clinical indications; clinical protocols; consents.

With specific regard to a commercial sponsor of an IND this Proposed Rule would, in fact, provide a disincentive to continue to conduct clinical research if its competitive information would be released publicly by FDA at such an early stage. The burden imposed by the proposed rule will likely drive sponsors conducting clinical trials to locations outside of the U.S., where the burdensome disclosure of sensitive information at such an early development stage is not required

3. Burden for Sponsors—Timing and interpretability are key issues, not types of data.
Under current Freedom of Information Act (FOIA) requirements, FDA may release IND information at the time that the license is issued for the product candidate in question after careful risk-benefit consideration of all data in an application.

This Proposed Rule imposes substantial burden on sponsors, both in terms of determining what must be disclosed under this Proposed Rule and in creating and submitting redacted copies of information provided to FDA, at a time much earlier in development of those data for the product candidate than is currently done. Indeed, this unusual requirement to disclose IND information at this early stage, would require that small scale studies be analyzed in isolation and that their results be extrapolated, perhaps inappropriately, to medical practice prematurely. One unintended effect of this early analysis might be unwarranted enthusiasm for products where evidence of adverse experiences can not adequately be assessed.

Merck maintains that information readily disclosable for most sponsors at the end of the development process, (ie. licensure), would not be acceptable to release at the beginning of the process (filing of the IND). In addition, disclosure at the filing of the IND would signal to competitors the direction of a sponsors research at a critical point in clinical trial recruitment, while disclosure at the point of licensure would continue to provide the intellectual property protections heretofore assured under the FD&C Act and its regulations.

4. Amending existing regulations may satisfy same need, in more limited fashion.
Why is FDA promulgating a new Proposed Rule which sharply contrasts with existing regulations, that broadly prohibit disclosure of information contained in IND application? FDA is barred from disclosing the existence of the IND unless it has been publicly disclosed or acknowledged by the sponsor. See 21 C.F.R. §§ 601.50 and 601.51. However, after a biologics license has been issued, all safety and effectiveness information and data and certain other information generally may be disclosed. See id.

The Proposed Rule seeks to overturn this broad prohibition. Instead of maintaining the confidentiality of the information, FDA would generally disclose much of the information presented by sponsors in IND submissions. See 66 Fed. Reg. 4705-06. Further, the burden would rest on the sponsor to justify withholding information.

Surprisingly, FDA states that sponsors have routinely publicly disclosed the information covered by the Proposed Rule, and that such information therefore cannot be considered confidential. FDA then states: "The fact that these types of information cannot be considered confidential is the principal basis for issuing this proposed rule." 66 Fed. Reg. 4693. If FDA is correct, then the Proposed Rule is unnecessary, since, under existing regulations, FDA can release information that has otherwise been publicly disclosed.

5. FDA exceeds its authority in release of IND information.

In the Proposed Rule, FDA proposes to extend its legal authority beyond its mandate to allow the release of information earlier than at the licensing point.

(A) Section 113 of the Food & Drug Modernization Act (FDAMA) which is cited, affects the collection of clinical trials information into a database at NIH which would allow practitioners and patients to learn about clinical trials for serious and life-threatening conditions for their potential enrollment. In comments to the Office of Management and Budget (OMB), dated December 11, 2000 (See Appendix 1), Merck has questioned FDA's over-interpretation of that provision of FDAMA, in which FDA proposed to include in the NIH database information on all clinical trials, not just those for serious and life-threatening conditions as intended by the law. In summary, Merck commented that overloading this database with extraneous information will discourage rather than encourage participation in critical trials, due to inability to find and interpret relevant information.

Further, it should be noted that FDAMA 113 does not address prophylactic or therapeutic products which are included within the purview of this Proposed Rule affecting gene therapies and xenotransplantation products.

(B) A recent court decision which requires FDA to simultaneously release to the public information provided to FDA advisory committees for drug product applications has been narrowly interpreted to not apply to similar release for biologicals or therapeutics advisory committees which would ordinarily consider FDA applications pertaining to gene therapies. In addition, this court decision does not apply to release of information to any advisory committees of other Federal agencies, such as the NIH Recombinant DNA Advisory Committee (RAC).

In this Proposed Rule, FDA implies that commercial sponsors who now voluntarily submit clinical protocols to the NIH RAC, may be required to submit clinical protocols for gene therapies and xenotransplantation products to the RAC as a matter of course. This would effectively apply an additional layer of regulatory scrutiny by NIH to that of FDA for commercially-sponsored products, where no significant problems have been reported.

6. Significant impact on licensing agreements and other collaborations.

From the perspective of license agreements and collaborations, a number of issues arise with a requirement to disclose information on efficacy and safety:

(A) Many currently existing agreements, which Merck has in place for licensing and collaboration arrangements, do not permit Merck to disclose confidential information provided from the outside party. To comply with the proposed regulations, Merck will be required in many cases to go back to the outside organization to request permission to disclose the outside party's information publicly. They may not agree to such disclosure and thus a product candidate could be in jeopardy.

(B) If the regulation goes into effect, it may serve as a barrier to Merck in obtaining confidential efficacy and safety data from a licensing partner or potential licensing partner.

They might be reluctant to disclose information because of what might need to be revealed publicly in the future. It will compromise Merck's conducting full diligence reviews and possible decisions about a licensing candidate.

7. Comments on Definitions / Implications for New Technologies.

In response to FDA's specific request for recommendations regarding the inclusion of viral and cellular products and their derivatives (that do not contain genetic material engineered into the product for therapeutic purposes) within its definition of gene therapy, Merck strongly believes that vaccines in general (whether DNA-based or viral-based) not be defined as gene therapy products. Defining vaccines as gene therapy products is scientifically inaccurate and incongruous. The intent of vaccines is to stimulate host responses to viral products transiently expressed; in contrast, gene therapy goals are to permanently replace altered functions by prolonged expression of transferred human products.

8. FDA resources and timing requirements for review and exposure of disclosable materials.

FDA's FOIA staff who redact materials before FDA advisory committee meetings have strict guidance regarding redaction rules and the timing of release of disclosable materials. Merck recommends that before this Proposed Rule proceeds further to implementation, if at all, that similarly strict and specific guidance be developed for sponsors and for FDA staff to understand the timing and types of information that will be exposed.

It can be expected that the volume of informational materials to be exposed under this Proposed Rule will far exceed FDA's ability to control it, since these materials are not simple and will require continuous and repeated back-up information to support their understanding and use.

Conclusions

All clinical trials, not just those for gene therapies, xenotransplantation products and any new emerging technology, are inherently risky. This Rule proposes to expose IND information from commercial regulatory filings for the purpose of reducing the risks in non-commercially sponsored clinical trials, but with little, if any, evidence that that objective will be met. Exposure of those data, heretofore, only released for specific and limited purposes will not prevent problems currently experienced in non-commercial clinical research, will confound decision-making regarding enrollment in these trials, and in all likelihood will cause several unintended effects that will stifle clinical research using new technologies in the future.

It is Merck's position that the scope and definition of the Proposed Rule require modification and reevaluation with respect to burden on sponsors both in terms of determining what must be disclosed and redacted. Further, the definition of gene therapy should more clearly exclude prophylactic and therapeutic DNA and adenovector based vaccines. Overall, this proposed rule for Disclosure of IND information is a troubling precedent to set and should be carefully reconsidered.

Clinical trials may be assumed to contain inherent risks and once the totality of the information is available, then FDA will make the decision about their risks and benefits. Clinical research of all products should be treated with the same amount of diligence and careful review regardless of

the method of creation (or manufacture) of the products being tested.

We welcome the opportunity for further comments.

Sincerely,

Henrietta N. Ukwu, MD, FACP
Vice President
Worldwide Regulatory Affairs
Vaccines/Biologics

Attachment (1)

FEDERAL EXPRESS

Attachment 1

Bonnie J. Goldmann, M.D.
Vice President
Regulatory Affairs

Merck & Co., Inc.
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2383
215 652 5000

MERCK
Research Laboratories

December 11, 2000

Office of Information and Regulatory Affairs
Attention: Wendy Taylor
Desk Officer for FDA
OMB
New Executive Office Building
725 17th Street NW., Rm 10235
Washington, DC 20503

RE: [Docket No. 00D-1033]
Notice: Agency Information Collection Activities: Submission for OMB Review: Comment Request; Draft Guidance for Industry on Information Program on Clinical Trials for Serious or Life-Threatening Diseases; Establishment of a Data Bank.

Merck & Co., Inc, is a leading worldwide, human health product company. Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds or potential drug candidates at one time through comprehensive, state-of-the-art R & D programs that include basic research and discovery, developmental studies in animals, manufacturing quality assurance testing, and, finally, human clinical research.

In the course of bringing product candidates through developmental testing Merck is well versed in all aspects of the design and conduct of clinical trials on a wide range of products including those intended to evaluate the efficacy of products for serious or life-threatening diseases. For these reasons, we are very interested and well qualified to comment on the Food and Drug Administration's (FDA's) proposed collection of information cited above.

Background

- The Food and Drug Administration Modernization Act (The Modernization Act) (Public Law 105-115) was enacted in November, 1997. Section 113 of the Modernization Act (Information Program on Clinical Trials for Serious or Life-threatening Diseases) required the Secretary of Health and Human Services, to establish, maintain, and operate a data bank of information on clinical trials for drugs for *serious or life-threatening diseases and conditions* (hereafter referred to as the 'Data Bank').
- The FDA issued a draft guidance to industry in March, 2000, in which it provided recommendations to sponsors of investigational new drug applications on submitting information to the Data Bank; that was the "Draft Guidance for Industry on Information

Program on Clinical Trials for Serious or Life-Threatening Diseases: Establishment of a Data Bank" [hereafter referred to as The Draft Guidance].

- On November 9, 2000, FDA published a notice announcing that a proposed collection of information pertaining to the *voluntary submission* of information to the Data Bank pertaining to studies that are not trials to test effectiveness of *not for serious or life-threatening diseases* had been submitted to the Office of Management and Budget for review and clearance under the Paperwork Reduction Act of 1995 [hereafter referred to as The Notice].

Comments on The Notice

Merck supports the concept of increased patient access to information on clinical trials for serious or life-threatening diseases provided under section 113 of the Food and Drug Administration Modernization Act (the Modernization Act). Merck has serious reservations about the voluntary inclusion in the Data Bank of information on clinical trials that are not for treatment of serious or life-threatening diseases for the following reasons:

1. Section 113 includes no provision for the voluntary submission of information on clinical trials of drugs that are not for serious or life threatening conditions. The inclusion of this extraneous information in the Data Bank has the potential to diminish the intended usefulness of the Data Bank to the patients for whom the statutory provision was enacted. The reasons for this include:

a) The more complicated and cluttered the Data Bank becomes with information unrelated to the serious or life-threatening diseases or conditions it was established to contain, the less likely health care providers will be able to find information relevant and beneficial to their most seriously ill patients.

b) Allowing information into the Data Bank on studies for other than the treatment of serious or life-threatening diseases or conditions may result in it becoming a tool for sponsors to "advertise" drug trials to accelerate recruitment.

c) The negative impact of the sheer volume of voluntary submissions on the resources necessary to "establish, maintain, and operate" the Data Bank for its intended purpose may severely compromise the ability of the Secretary to assure the currency, quality, accuracy, and availability of information needed by the patients with the fewest alternatives. By FDA's own estimate in The Notice, the annual number of protocols voluntarily submitted for studies not for the treatment of serious or life-threatening conditions (3 120) well exceeds the number for serious or life-threatening conditions (2,386) required to be submitted under Section 113. Similarly, the annual number of protocol amendments (necessary to keep information in the Data Bank current) for voluntary submissions (19,720) will exceed the annual number of required submissions to the Data Bank (14,940).

2. The Notice of the submission to OMB of the proposed collection of information to be voluntarily submitted to the Data Bank regarding clinical trials of drugs that are not for serious or life threatening diseases or conditions implies that the collection is authorized under section 113 of The Modernization Act when, in fact, such submissions are only described in FDA's Draft Guidance.

Conclusion

MRL recognizes that The Notice deals with voluntary submission of information. As such, sponsors may choose not to submit information on the kinds of studies described in The Notice. However, the more likely outcome would be the inclusion of extraneous information in a Data Bank, created by the express terms of The Modernization Act as an "information repository on trials for serious or life-threatening diseases." This unintended use of the Data Bank has the potential to seriously compromise the establishment, maintenance, and operation of the Data Bank for the serious purpose it was intended. Furthermore, information on studies that are not intended to evaluate the effectiveness of investigational drugs for serious or life-threatening conditions will make it difficult for patients and providers who lack alternatives among conventional therapies to find the vital information the Data Bank was established by statute to provide and may be a disincentive to its further use.

For the reasons stated above, the proposed collection of information described in The Notice should be reconsidered absent evidence that the collection of such information and its inclusion in the Data Bank will not compromise the clear intent for which Congress established the Data Bank under the provisions of Section 113.

We welcome the opportunity to comment on this notice.

Sincerely,

Marie A. Gray for Bonnie Goldmann

Bonnie J. Goldmann, MD

From: CARLO RUSSO, MD (610)397-7610
MERCK AND CO., INC
P O BOX 4, UN B-121
SUMNEYTOWN PIKE
WEST POINT, PA, 19486

SHIPPER'S FEDEX ACCOUNT #

FedEx.

To: HFA-305 (610)397-7611
Dockets Management Branch, FDA
5630 Fishers Lane
Room 1061
Rockville, MD, 20852

SHIP DATE: 09MAR01
WEIGHT: 1 LBS

Ref:

DELIVERY ADDRESS
TRK # 7904 9222 4701 FORM 0201

PRIORITY OVERNIGHT

MON
AA
Deliver by:
12MAR01

20852-MD-US

IAD
ZM GAIA