

February 11, 2000

8 7 7 6 '00 FEB 14 A8:49

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



RE: Docket No. 99N-1852

Proposed Rule: Postmarketing Studies for Human Drugs and Licensed Biological Products

Merck & Co., Inc, is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$2 Billion, annually, on worldwide Research and Development (R & D). 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.

Research, by its nature, is a multidisciplinary and highly risk-intensive business. It depends upon many variables, including: prolific source materials, first class talent, adequate funding, efficient and effective quality processes and procedures, and a predictable regulatory environment.

Merck's research scientists ensure that our research process continues to identify medically important product candidates from thousands of chemical and molecular entities screened each year. Only one in ten of these research product candidates is selected to enter the development programs. The medicines which Merck ultimately presents to worldwide health authorities for marketing approval are those that have met the highest technical standards available and those that are able to withstand the most critical regulatory review.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. Regulators must be reasonable, unbiased and efficient when they review the quality, effectiveness and safety of our products. It is in both of our interests to see that important therapeutic advances reach patients without unnecessary or unusual delays.

Merck has recently completed or is conducting large-scale post-marketing safety studies of three innovative vaccines: COMVAX® (Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine), VARIVAX® (Varicella Virus Vaccine Live [Oka/Merck]), and VAQTA® (Hepatitis A Vaccine, Inactivated). These studies are designed to evaluate different parameters such as long-term persistence

99N-1852

C4

**Proposed Rule: Postmarketing Studies for Human Drugs
and Licensed Biological Products**

of antibody and the potential for rare and unusual adverse events. Each of the post-marketing study protocols has been submitted to and approved by CBER. Merck has consistently provided CBER with annual reports of the progress of these post-marketing studies, via submissions to the PLA (VARIVAX®) or the IND (COMVAX® and VAQTA®). We are, therefore, interested in the proposed rule and believe that we are well qualified to comment on it constructively.

We commend FDA for the effort to issue a Rule that will ensure that all postmarketing studies are performed in accordance with commitments made at the time of licensure. In general, Merck supports the requirement for an annual report for post-marketing studies. However, Merck has serious concerns about specific portions of this policy as written and its impact on worldwide drug/vaccine development if the proposal is implemented as presently written.

POINTS OF CONCERN

1. Public Disclosure of Information - Inconsistency on the Extent of Public Disclosure

We note an inconsistency in the Proposed Rule between section II.C. (entitled “Content of Status Reports”), subsections 8.b and 9, and II.F. (entitled “Public Disclosure of Information”). Sections II.C.8.b and II.C.9 specify that the information to be reported in the proposed annual report is to be limited to patient accrual and study status. However, Section II.F states that in addition to patient accrual and study status, the FDA will also make the study protocol and the study results public. It is important that this inconsistency be clarified.

2. Public Disclosure of Information - Study Protocol

Merck’s clinical protocols are highly proprietary in terms of design and analytical plan. Details of these protocols have always been highly confidential because they are the result of the intellectual efforts of our personnel and would be of great interest to Merck’s competitors. We believe that the specific design of the study protocols of postmarketing studies should be protected to the same degree as other clinical protocols that are submitted to the FDA. We do recognize the value of sharing information on post-marketing studies with the public. Accordingly, Merck would like to propose that the sponsor of a postmarketing study supply a general description of the study for the express purpose of being made public under this rule.

3. Public Disclosure of Information - Study Results

We recognize the value in public dissemination of the results of completed studies, but it is Merck’s position that full Clinical Study Reports should not be made public because they are complex and extensive, and often contain information of commercial potential. It would be much more appropriate if the sponsor of the study would

prepare a brief summary of the study expressly for public disclosure that could be submitted with the full Clinical Study Report.

4. Public Disclosure of Information - Adverse Events

Section II.F of the Proposed Rule specifies that the FDA will make public “reports of unexpected (i.e. unlabeled) suspected adverse drug reactions”. Merck’s position is that many of the postmarketing studies are epidemiological in nature, and therefore, by design, capture all medical episodes that occur during the lives of the study population. We do not agree that publication of the reports of all unexpected, suspected adverse drug reactions from such studies are warranted because no scientifically-based conclusions can be drawn when safety reports are reviewed out of context of the study population and without regard to the appropriate controls. It is of course understood that if any new association is established between a drug/vaccine and a previously unknown adverse reaction, such information should be made public. However, we do not believe that annual reports are the appropriate vehicle for public disclosure of such information.

5. Implementation Plan

The proposals detailed in Section II.G.1 (entitled “Proposed Implementation Plan – Effective Dates”) specify that Annual Reports will be required based on the product’s anniversary date of U.S. approval. As noted previously, Merck has conscientiously submitted annual reports of postmarketing studies. However, the annual reports have been provided based on the anniversary of the study initiation. As conceded in Section II.G.1, in the first year after implementation of the Proposed Rule, Merck would be required to submit two “annual” reports. Obviously, the second of these annual reports would contain data from a time interval less than one year. Significant resources would be required at Merck to draft the second annual report, as well as at the FDA to review the report, which due to the limited data, would be of minimal value. For these reasons, Merck proposes that studies which are already underway at the time that the Rule is enacted and for which Annual Reports have always been submitted, adhere to the annual reporting cycle which has already been established for the given study.

SUMMARY

In conclusion, the requirement of an Annual Report for post-marketing studies is reasonable to ensure that commitments made at the time of licensure are met. Nonetheless, it is critical that detailed study protocols and Clinical Study Reports not be made public. Annual public disclosure of all reports of unexpected drug reactions are inappropriate for epidemiological studies such as are now required upon licensure of most drugs and vaccines. Finally, post-marketing studies which are underway and for which annual reports are already being provided should continue to use the annual reporting cycles that are already established.

**RE: [Docket No. 99N-1852
Proposed Rule: Postmarketing Studies for Human Drugs
and Licensed Biological Products**

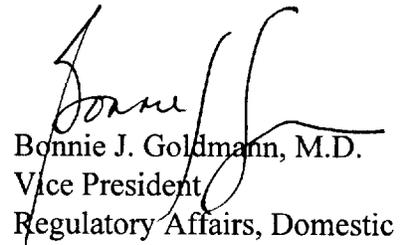
Page 4

We appreciate the opportunity to comment on the Proposed Rule entitled "Postmarketing Studies for Human Drugs and Licensed Biological Products" and would welcome the opportunity to discuss it further.

Sincerely,



Henrietta N. Ukwu, M.D.
Vice President
Worldwide Regulatory Affairs
for Vaccines and Biologics



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

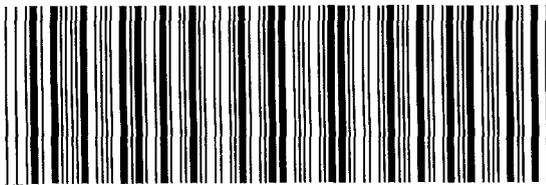
1 From
 Date 2/11/00 Sender's FedEx Account Number 1024-1778-0
 Sender's Name Bonnie J. Goldmann, M.D. Phone (610) 397-2383
 Company MERCK SHARP & DOHME
 Address 5 SENTRY PKWY WEST BLA-20
 City BLUE BELL State PA ZIP 19422

2 Your Internal Billing Reference Information

3 To
 Recipient's Name Dockets Mgmt Branch Phone ()
 Company Food and Drug Administration
 Address 5630 Fishers Lane Room 1061
 City Rockville State MD ZIP 20852

For HOLD at FedEx Location check here
 Hold Weekday 31 (Not available with FedEx First Overnight)
 Hold Saturday (Not available at all locations) (Available for FedEx Priority Overnight and FedEx 2Day only)

For WEEKEND Delivery check here (Extra Charge Not available at all locations)
 Saturday Delivery 33 (Available for FedEx Priority Overnight and FedEx 2Day only)
 NEW Sunday Delivery (Available for FedEx Priority Overnight only)



8 1 0 4 9 5 6 6 3 6 5 6

4a Express Package Service Packages under 150 lbs. Delivery commitment may be later in some areas.
 FedEx Priority Overnight (Next business morning) 5 FedEx Standard Overnight (Next business afternoon)
 FedEx First Overnight (Earliest next business morning delivery to select locations) (Higher rates apply)
 FedEx 2Day (Second business day) 20 FedEx Express Saver (Third business day) (Up to 3 business days)
 FedEx Letter Rate not available. Minimum charge: One pound rate.

4b Express Freight Service Packages over 150 lbs. Delivery commitment may be later in some areas.
 FedEx Overnight Freight (Next business day) 8 FedEx 2Day Freight (Second business day) 83 FedEx Express Saver Freight (Up to 3 business days)
 (Call for delivery schedule. See back for detailed descriptions of freight services.)

5 Packaging FedEx Letter FedEx Pak FedEx Box FedEx Tube Other Pkg.
 XXX

6 Special Handling (Shipper's Declaration required)
 Does this shipment contain dangerous goods? No Yes Shipper's Declaration (Not required)
 Dry Ice (Dry Ice, 9 UN 1845) x kg. CA Cargo Aircraft Only
 Dangerous liquids cannot be shipped in FedEx packaging.

7 Payment Obtain Recipient FedEx Account No.
 Bill to: Sender (Account No. is required) Recipient Third Party Credit Card Cash/Check
 (Enter FedEx Account No. or Credit Card No. below)

FedEx Account No. _____ Exp. Date _____
 Credit Card No. _____

Total Packages _____ Total Weight _____ Total Charges _____

*When declaring a value higher than \$100 per shipment, you pay an additional charge. See SERVICE CONDITIONS, DECLARED VALUE, AND LIMIT OF LIABILITY section for further information.
 Credit Card Auth.

8 Release Signature

This signature authorizes Federal Express to deliver this shipment without obtaining a signature and agrees to indemnify and hold harmless Federal Express from any resulting claims.

321

WCSL 1296 Rev. Date 7/98 Part #153023ps

0085547061