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Health, Education, and
Human Services Division

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August 13, 1999

The Honorable Thomas J. Bliley, Jr.
Chairman
The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives

The Honorable Fred Upton
Chairman
The Honorable Ron Klink
Ranking Minority Member
Subcommittee on Oversight and Investigations
Committee on Commerce
House of Representatives

Subject: Mutual Recognition Agreement: Update on the Food and Drug Administration's Progress in Assessing Equivalency of European Union Pharmaceutical Good Manufacturing Practice Regulatory Systems

A mutual recognition agreement (MRA) between the United States and the European Union[1] became effective December 1, 1998. MRA affects billions of dollars in trade and includes six annexes,[2] one of which covers good manufacturing practice (GMP) inspections of pharmaceutical facilities. Specifically, the pharmaceutical GMP annex provides that the United States will assess whether the pharmaceutical GMP regulatory systems[3] in the 15 European Union member states are equivalent to that of the United States during a 3-year transition period beginning December 1, 1998. An

[1]The European Union consists of 15 countries, or member states: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

[2]The annexes contain specific provisions related to the products, programs, and procedures covered by MRA.

[3]Under Article 1 of the pharmaceutical GMP annex to MRA, a pharmaceutical GMP regulatory system is referred to as the body of legal requirements for GMPs, inspections, and enforcements that ensure public health protection and legal authority to ensure adherence to these requirements.

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appendix to MRA's pharmaceutical annex also provides criteria that the United States and the European Union are to use to assess the equivalence of their respective regulatory systems. (See enclosure I.) The Food and Drug Administration (FDA)—which conducts GMP inspections in the United States and abroad to ensure the safety and quality of domestic and imported pharmaceutical products[4]—is responsible for making these assessments.

This correspondence responds to your request that we provide an update on the status of FDA's implementation of MRA. In an earlier correspondence on FDA's progress assessing pharmaceutical inspection programs, we reported that nearly 3 months into the transition period, FDA did not have a comprehensive plan for conducting equivalence assessments of member states' pharmaceutical GMP regulatory systems.[5] At that time, FDA also could not provide us an update of the estimated costs and resources needed to implement MRA. FDA officials told us that an update of the plan for making assessments of equivalence and cost estimates would not be available until March 1999. Given your concerns about FDA's lack of progress in developing plans to implement MRA, you asked us to continue to monitor FDA's progress. Specifically, you asked us to determine (1) the progress FDA has made in developing a plan for assessing equivalence of European Union member states' pharmaceutical GMP regulatory systems; (2) the amounts FDA spent, from October 1994 through March 1999, on negotiating and implementing MRA and the amount FDA plans to spend on making assessments of equivalence; and (3) the status of the European Union's efforts to coordinate with FDA to implement MRA.

In summary, FDA's MRA implementation plan establishes a framework for making assessments of equivalence of European Union member states. The implementation plan also includes a strategy for making assessments of equivalence and estimating the costs and resources needed to implement MRA. However, FDA has not yet determined how it will use the criteria in the pharmaceutical GMP annex to assess whether the regulatory systems of the European Union member states are equivalent to FDA's regulatory systems. FDA could only provide rough estimates of the costs to negotiate and prepare for the implementation of MRA because it does not maintain a system for tracking the time staff spent on MRA-related activities. According to FDA estimates, FDA will require about $10 million—including the cost of about 125 full-time equivalent employees—during the transition period and first operational year of

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[4]We use pharmaceutical products to refer to pharmaceuticals imported in finished dosage forms as well as bulk drug substances (for example, active pharmaceutical ingredients or bulk pharmaceutical chemicals).

[5]Mutual Recognition Agreement: Food and Drug Administration's Progress in Assessing Equivalency of European Union Pharmaceutical Inspection Programs (GAO/HEHS-99-71R, Feb. 26, 1999).

MRA.[6] Meetings of the committees established to oversee implementation of the pharmaceutical GMP annex and MRA have resulted in the exchange of draft plans for implementing the annex and making assessments of equivalence and clarification of the GMP definition.

Our work was conducted between April 1999 and August 1999 in accordance with generally accepted government auditing standards. Our methodology is described in enclosure II.

BACKGROUND

MRA includes six annexes covering telecommunications equipment, electromagnetic compatibility, electrical safety, recreational craft, medical devices, and GMP inspections of pharmaceutical facilities. The pharmaceutical annex to MRA provides that during a 3-year transition period, which became effective on December 1, 1998, FDA will assess the pharmaceutical GMP regulatory systems of the 15 European Union member states. For countries determined by FDA to have systems equivalent to the United States', the annex provides for the exchange and endorsement of U.S. and European Union pharmaceutical GMP inspection reports after the transition period. According to FDA, such an exchange will help it redirect some of its inspection resources to foreign pharmaceutical facilities that manufacture drug products not covered by such agreements, thereby providing a more responsive level of U.S. consumer protection in the global marketplace.

During the transition period, FDA and member states of the European Union will undertake equivalency assessments of their respective regulatory systems. According to the pharmaceutical GMP annex, equivalence is achieved when regulatory systems cover criteria specified in the annex and demonstrate the ability to consistently apply the criteria. These include criteria for evaluating the equivalence of the regulatory authority, professional standards and conduct, administrative controls, inspection competence, and systems of enforcement and surveillance. In addition, the parties will develop a common inspection report format, establish an alert system for the exchange of information on the safety of drug products, and conduct joint training sessions for inspectors. MRA also provided for the establishment of the Joint Sectoral Committee to monitor the activities under both the transitional and operational periods of the pharmaceutical GMP annex and a joint committee to oversee the functioning of the six MRA annexes.

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[6]The operational period begins after the end of the transition period and continues for the life of the annex. Activities during the period include sharing alert information and establishment inspection reports, endorsement of establishment inspection reports, and monitoring equivalence.

In February 1998, before MRA was ratified, FDA prepared an initial implementation plan that provided an organizational and procedural framework for implementing the pharmaceutical GMP annex. The plan identified the organizational groups within FDA responsible for carrying out various aspects of the annex and provided a schedule of general activities and milestones for implementing MRA. However, the plan did not include specific information on the tasks FDA would perform to conduct assessments of equivalence, how those tasks would be completed, or estimates of the costs and resources necessary to implement MRA. The final regulation to implement MRA's pharmaceutical annex was published on November 6, 1998, and became effective on December 7, 1998. On April 13, 1999, FDA provided us with a revised implementation plan that supplements the February 1998 implementation plan.

FDA'S PLAN FOR EQUIVALENCY ASSESSMENTS

FDA's April 1999 implementation plan generally provides for the same organizational and procedural framework for implementing the pharmaceutical GMP annex as the February 1998 implementation plan. However, the revised plan for implementing the annex includes FDA's most recent strategy for initiating assessments of equivalence, including milestones for completing MRA-related activities and estimates of costs and resources necessary during the transition period (fiscal year 1999 through 2001) and the first year of the operational period (fiscal year 2002). According to FDA officials, the implementation plan does not account for all of the potential scenarios that may result from conducting assessments of equivalence because this process is new to the agency. Nevertheless, FDA intends to carry out these assessments in a way that allows the agency to adjust the implementation plan as it gains experience, while ensuring public health protection.

The first step in FDA's implementation plan is to initiate document reviews of the member states' pharmaceutical GMP regulatory systems. These will include reviews of the statutes, regulations, inspection and sampling procedures, and training requirements used by each member state to determine whether they are equivalent to FDA's. In preparing for these assessments, FDA developed a document that describes aspects of its pharmaceutical GMP regulatory system for each criterion listed in MRA, which serve as benchmarks for assessing the European Union member states' regulatory systems. In July 1999, FDA made the document available to the European Union member states and requested that they provide information on their pharmaceutical GMP regulatory systems by August 1999.

Upon completing the document reviews, FDA will conduct on-site inspections in the member states to verify that the documented procedures of the regulatory systems are in place. In those member states that appear to have equivalent regulatory systems, FDA will conduct inspections to assess the performance of the inspectors' investigations of drug products and process types, as well as the equivalence of the systems of enforcement and surveillance. These inspections will be completed during the transition period.

FDA's implementation plan projects that it will complete the assessments of equivalence for each member state's regulatory system by the end of the transition period. These assessments will include establishing the equivalence of member states' legal and administrative processes, the competence of their inspectors, and the adequacy of their enforcement and surveillance systems. However, FDA's projection assumes that it will not be necessary to evaluate each member state for every phase of the assessment process because significant deficiencies may be identified in a member state's regulatory system during the initial phases of the assessment process. When significant deficiencies are identified, FDA intends to cease further evaluation of a member state until these deficiencies are corrected. FDA expects that the experienced gained from its early evaluations will help the agency refine its procedures and ultimately result in later assessments being completed in less time than earlier ones.

FDA has not established an order for making assessments of equivalence among the member states. However, to decide the order in which it will make assessments of member states, FDA plans to consider factors such as the volume of drugs imported into the United States from a member state, the number of manufacturing facilities in a member state that market in the United States, and the results of past FDA inspections. According to FDA officials, several FDA teams will apply the criteria in the pharmaceutical GMP annex and make initial assessments of equivalence based on their expertise and input from other offices within the agency. The teams' proposals of equivalence will be presented to and endorsed by the designated committees responsible for MRA implementation.

Although FDA has made progress in preparing for the implementation of MRA since February 1998—when it issued its first implementation plan—the April 1999 plan still does not include information on how it will apply the annex's approximately 30 criteria to the regulatory systems of member states and render decisions of equivalence. In our view, the implementation plan should clearly explain how the criteria should be applied to ensure that FDA can make consistent assessments and equivalence determinations among member states.

FDA officials acknowledged that they have not yet identified the attributes of its regulatory system that should be included in the regulatory systems of member states in order for them to be considered equivalent. However, these officials stated that the teams making equivalence assessments will decide how to make these comparisons and present their findings during the initial equivalence determinations. The teams' procedures and decisions will be documented for use in making subsequent equivalence reviews. According to FDA officials, a final judgment of equivalence will not be made until the end of the transition period to ensure ample opportunity to review early decisions and ensure that all member states are treated equitably in the assessment process.

FDA'S ESTIMATES OF COSTS AND RESOURCES RELATED TO MRA IMPLEMENTATION

Because it does not have a system for tracking the time individual personnel spend working on specific assignments, FDA can not provide a precise accounting of the amount the agency has spent on the negotiation and early implementation of MRA's pharmaceutical GMP annex. Nevertheless, FDA estimated that from October 1994 through March 1999, it spent approximately $3 million, including the costs for 33 full-time equivalent (FTE) employees, to participate in various meetings related to the negotiation of MRA and to prepare MRA regulation. FDA also estimated that it additionally spent about $22,000 in travel expenses related to MRA negotiations. To develop its estimates, FDA relied heavily on the recollections of key participants in MRA negotiations and a list of participants that attended MRA-related meetings.

FDA's April 1999 implementation plan includes estimates of the costs and resources that it will need during the transition period (fiscal year 1999 through fiscal year 2001) and the first year of the operational period (fiscal year 2002).[7] However, FDA officials acknowledged that these estimates are preliminary projections that may change as it gains experience implementing MRA.

According to the April 1999 implementation plan, FDA will spend about $10 million on MRA—about $8 million during the transition period and about $2 million in the first year of the operational period. FDA plans to spend most of these funds on FTEs to carry out MRA-related activities—about $7.1 million during the transition period and about $1.3 million during the first year of the operational period. These MRA-related activities will include audits of the regulatory systems of member states, training of FDA personnel to conduct inspections and make assessments of the performance and competence of inspectors in conducting drug investigations in member states, and formal committee meetings and public meetings. In addition, FDA estimates it will spend $977,000 during the transition period and $350,000 during the first year of the operational period for non-personnel-related MRA expenses, such as travel and translation of foreign documents.

To carry out its responsibilities under MRA, FDA intends to use resources from several organizational groups within the agency. The plan estimates that a total of about 125 FTEs are required during the transition period and the first year of the operational period, 105 FTEs and 20 FTEs, respectively. During the transition period, FDA estimates that it would use an average of about 35 FTEs per year, ranging from about 17 FTEs in fiscal year 1999 to about 46 FTEs in fiscal year 2001.

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[7]FDA could not reconcile the overlap between the estimated cost to implement the MRA for fiscal year 1999 with the estimated amount of funds that were spent on travel and resources to negotiate and implement the MRA during the first 6 months of fiscal year 1999.

EUROPEAN UNION AND FDA COORDINATION

According to European Union officials, responsibility for implementing work on the pharmaceutical GMP annex of MRA has been delegated to the European Agency for the Evaluation of Medicinal Products (EMEA). EMEA is coordinating the resources in member states to ensure the equivalency assessments of FDA's pharmaceutical GMP regulatory system. Since December 1998, when the transition period began, FDA and European Union representatives have held several telephone conversations to discuss preliminary plans and responsibilities for conducting equivalency assessments. European Union officials acknowledged that to execute MRA, there are several issues that will require FDA cooperation, including developing a mutually agreed upon inspection report format and a joint alert system, which are currently under discussion.

The European Union expects that these issues will be discussed and resolved through formal meetings of the Joint Sectoral Committee, the first of which was held on May 18 and 19, 1999. At that meeting, FDA and European Union representatives discussed implementation of the pharmaceutical GMP annex. Specifically, they discussed methods to facilitate coordination between the United States and European Union, issues concerning the safeguarding of confidential documents, the establishment of a joint work group to develop elements of a two-way alert system to protect public health, and draft plans for making assessments of equivalence.

On June 11, 1999, the European Union and United States held a joint committee meeting to review the progress of MRA implementation. During the meeting, the resolution of GMP's definition was discussed. FDA and the European Union agreed on an approach to accommodate their different views on what should be included in the definition. The committee endorsed this approach, and the European Union will proceed with its process to initiate the necessary change in the agreement. According to FDA officials, an identical GMP definition is not essential because the focus of equivalency assessments is on whether the pharmaceutical GMP regulatory systems of the European Union member states are equivalent to FDA's. As such, the first paragraph[8] of the GMP definition contained in the text of MRA will be attributed to

[8]FDA defines GMPs to mean "the requirements found in the respective legislations, regulations, and administrative provisions for methods to be used in, and the facilities or controls to be used for[,] the manufacturing, processing, packing, and/or holding of a drug to [en]sure that such drug meets the requirements as to safety, and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess."

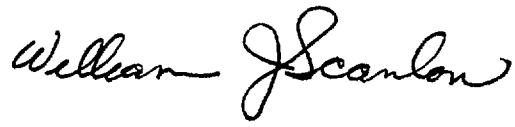
FDA and the second paragraph[9] to European Union member states.

AGENCY COMMENTS

FDA officials reviewed a draft of this report. FDA generally found the report to be accurate and complete and made several technical comments clarifying aspects of the agency's implementation of the pharmaceutical GMP annex, which have been incorporated as appropriate.

We are sending copies of this report to the Honorable Donna E. Shalala, Secretary of Health and Human Services; the Honorable Jane E. Henney, M.D., the Commissioner of FDA; and others who are interested. If you have any questions about this correspondence, please call me at (202) 512-7114 or John Hansen at (202) 512-7105. Other major contributors included Darryl Joyce and Claude Hayeck.

Sincerely yours,



William J. Scanlon
Director, Health Financing
and Public Health Issues

Enclosures

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[9]Member states define GMPs as "that part of quality assurance that ensures that products are consistently produced and controlled to quality standards. For the purpose of this annex, GMPs include therefore the system whereby the manufacturer receives the specifications of the product and/or process from the marketing authorization/product authorization or license holder or applicant and ensures the product is made in compliance with its specifications."

CRITERIA FOR ASSESSING EQUIVALENCE OF PHARMACEUTICAL GMP REGULATORY SYSTEMS UNDER MRA BETWEEN THE UNITED STATES AND THE EUROPEAN UNION

Appendix 4 of the pharmaceutical GMP annex of MRA establishes criteria, listed below, for making equivalency assessments of the U.S. and European Union regulatory systems. According to MRA, equivalence is achieved by having regulatory systems that cover these criteria and a demonstrated pattern of consistent performance in accordance with the criteria.

I. Legal/Regulatory Authority and Structures and Procedures Providing for Post- and Preapproval Inspections

- Appropriate statutory mandate and jurisdiction
- Ability to issue and update binding requirements on GMPs and guidance documents
- Authority to make inspections, review and copy documents, and to take samples and collect other evidence
- Ability to enforce requirements and to remove products found in violation of such requirements from the market
- Substantive current good manufacturing requirements
- Accountability of the regulatory authority
- Inventory of current products and manufacturers
- System for maintaining or accessing inspection reports, samples, and other analytical data, and other firm/product information relating to matters covered by this sectoral annex

II. Mechanism in Place to Ensure Appropriate Professional Standards and Avoidance of Conflicts of Interest Administration of the Regulatory Authority

III. Administration of Regulatory Authority

- Standards of educational/qualification and training
- Effective quality assurance system measures to ensure adequate job performance
- Appropriate staffing and resources to enforce laws and regulations

IV. Conduct of Inspections

- Adequate preinspection preparation, including appropriate expertise of investigator/team, review of firm/product and databases, and availability of appropriate inspection equipment
- Adequate conduct of inspection, including statutory access to facilities, effective response to refusals, depth and competence of evaluation of

operations, systems, and documentation; collection of evidence; appropriate duration of inspection and completeness of written report of observations to firm management

- Adequate postinspection activities, including completeness of inspector's report; inspection report review, where appropriate; conduct of follow-up inspections and other activities, where appropriate; and assurance of preservation and retrieval of records

V. Execution of Regulatory Enforcement Actions to Achieve Corrections Designed to Prevent Future Violations and to Remove Products Found in Violation of Requirements From the Market

VI. Effective Use of Surveillance Systems

- Sampling and analysis
- Recall monitoring
- Product defect reporting system
- Routine surveillance inspections
- Verification of approved manufacturing process changes to marketing authorizations/approved applications

VII. Additional Specific Criteria for Preapproval Inspections

- Satisfactory demonstration through a jointly developed and administered training program and joint inspections to assess the authorities' capabilities
- Preinspection preparation includes the review of appropriate records, including site plans and drug master file or similar documentation to enable adequate inspections
- Ability to verify chemistry, manufacturing, and control data supporting an application is authentic and complete
- Ability to assess and evaluate research and development data as scientifically sound, especially transfer technology of pilot, scale-up, and full-scale production batches
- Ability to verify conformity of the on-site processes and procedures with those described in the application
- Review and evaluate equipment installation, operational and performance qualification data, and evaluate test-method validation

METHODOLOGY

In examining FDA's implementation of the pharmaceutical GMP annex, we reviewed MRA to determine the annex's requirements. To obtain information on FDA's plan for making equivalence determinations with European Union member states, we met with FDA officials involved in implementing the pharmaceutical GMP annex. These included officials from the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, the Office of Regulatory Affairs, the Office of International Affairs, and the Office of Chief Counsel. We analyzed FDA's revised implementation plan of April 13, 1999, and compared it to the initial implementation plan of February 1998 to determine the progress made in implementing MRA. We also analyzed FDA's estimates of the costs to (1) negotiate and implement MRA from October 1994 through March 1999 and (2) implement MRA during the transition period (fiscal year 1999 through fiscal year 2001) and the first year of the operational period (fiscal year 2002). We interviewed European Union officials to discuss their coordination with FDA and reviewed correspondence of the designated committees of MRA to determine the progress made in implementing the agreement.

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