high degree of species, strain, and target organ specificity and by the existence of thresholds in the dose-response relationship. Mechanistic studies in recent years have permitted the distinction between effects that are specific to the rodent model and those that are likely to have relevance for humans. Progress has often been associated with increased understanding of species and tissue specificity. For example, receptor-mediated carcinogenesis is being recognized as of growing importance. Most of these advances are being made in the rat, and only rarely in the mouse.

6.3 Metabolic disposition.

Neither rats nor mice would seem, on metabolic grounds, to be a priori generally more suitable for the conduct of long-term carcinogenicity studies. However, much attention is now being given to pharmacokinetic-pharmacodynamic relationships and rapid progress is occurring in knowledge of the P–450 isozymes that mediate the biotransformation of drugs. Most of this research activity is confined to rats and humans. Therefore, in the near future at least, where specific information on the P–450 isozymes involved in biotransformation is critical for the evaluation, it appears that mice would be less likely to provide this mechanistic information.

6.4 Practicality.

Pertinent to the above two topics is the question of feasibility of investigative studies. Size considerations alone put the mouse at a severe disadvantage when it comes to the taking of serial blood samples, microsurgery/catheterization, and the weighing of organs. Blood sampling often requires the sacrifice of the animals, with the result that many extra animals may be needed when mice are subject to such investigations.

6.5 Testing in more than one species.

Most of the currently available short- and medium-term in vivo models for carcinogenicity testing involve the use of mice. In order to allow testing in more than one species for carcinogenic potential when this is considered important and appropriate, the rat will often be used in the long-term carcinogenicity study.

6.6 Exceptions.

Despite the above considerations, there may be circumstances under which the mouse or another rodent species could be justified on mechanistic, metabolic, or other grounds as being a more appropriate species for the long-term carcinogenicity study for human risk assessment (cf. section 4.2.1). Under such circumstances, it may still be acceptable to use the mouse as the short-term or medium-term model.

7. Evaluation of Carcinogenic Potential

Evidence of tumorigenic effects of the drug in rodent models should be evaluated in light of the tumor incidence and latency, the pharmacokinetics of the drug in the rodent models as compared to humans, and data from any ancillary or mechanistic studies that are informative with respect to the relevance of the observed effects to humans.

The results from any tests cited above should be considered as part of the overall ''weight of evidence,'' taking into account the scientific status of the test systems.

Notes

Note 1. Data from in vitro assays, such as a cell transformation assay, can be useful at the compound selection stage.

Note 2. If the findings of a short- or long-term carcinogenicity study and of genotoxicity tests and other data indicate that a pharmaceutical clearly poses a carcinogenic hazard to humans, a second carcinogenicity study would not usually be useful.

Note 3. Several experimental methods are under investigation to assess their utility in carcinogenicity assessment. Generally, the methods should be based on mechanisms of carcinogenesis that are believed relevant to humans and applicable to human risk assessment. Such studies should supplement the long-term carcinogenicity study and provide additional information that is not readily available from the long-term assay. There should also be consideration given animal numbers, welfare, and the overall economy of the carcinogenic evaluation process. The following is a representative list of some approaches that may meet these criteria and is likely to be revised in the light of further information.

(a) The initiation-promotion model in rodent. One initiation-promotion model for the detection of hepatocarcinogens (and modifiers of hepatocarcinogenicity) employs an initiator, followed by several weeks of exposure to the test substance. Another multi-organ carcinogenesis model employs up to five initiators followed by several months of exposure to the test substance.

(b) Several transgenic mouse assays, including the p53+/- deficient model, the Tg.AC model, the TgHras2 model, the XPA deficient model, etc.

(c) The neonatal rodent tumorigenicity model.

Note 4. While there may be a number of approaches that will in general meet the criteria described in Note 3 for use as the additional in vivo study, not all may be equally suitable for a particular pharmaceutical. The following are examples of factors that should be considered and addressed in the rationale:

1. Can results from the model provide new information not expected to be available from the long-term study that is informative with respect to hazard identification and/or risk assessment?

2. Can results from the model address concerns related to the carcinogenic process arising from prior knowledge of the pharmaceutical or compounds with similar structures and/or mechanisms of action? These concerns may include genotoxic, mitogenic, promotional, or receptor-mediated effects, etc.

3. Does the metabolism of the pharmaceutical shown in the animal model affect the evaluation of carcinogenic risk for humans?

4. Is adequate systemic or local exposure attained in relation to human exposure?

5. How extensively has the model been evaluated for its intended use? Prior to using any new in vivo methods in testing the carcinogenic potential of pharmaceuticals for humans, it is critical that the method be evaluated for its ability to contribute to the weight of evidence assessment. Many experimental studies are in progress (1997) to evaluate the new short or medium tests for carcinogenic potential. These include selected pharmaceuticals with known potencies and known mechanism of carcinogenic activity in rodents and also putative human noncarcinogens. When the results of these studies become available, it may be possible to offer more specific guidance on which of these tests have the most relevance for cancer assessment in humans.

Other ICH Guidances Cited

''S2A Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals.''

''S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals.''

''S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies.''

''S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies.''

''S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.''

Dated: February 13, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–4373 Filed 2–20–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Endocrinologic and Metabolic Drugs Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: Endocrinologic and Metabolic Drugs Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the agency on FDA regulatory issues.

Date and Time: The meeting will be held on March 12 and 13, 1998, 8 a.m. to 5 p.m.

Location: Holiday Inn Gaithersburg, Walker Room, Two Montgomery Ave., Gaithersburg, MD.

Contact Person: Kathleen R. Reedy or LaNise S. Giles, Center for Drug Evaluation and Research (HFD–21), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–5455, or FDA Advisory Committee Information Line, 1–800–

741–8138 (301–443–0572 in the Washington, DC area), code 12536. Please call the Information Line for up-to-date information on this meeting.

Agenda: On March 12, 1998, the committee will discuss a proposed draft of a guidance document for the development of drugs for the treatment of diabetes mellitis. On March 13, 1998, the committee will discuss New Drug Application 20–766, Xenical™, (orlistat tetrahydrolipstatin, Hoffman-LaRoche) for long term treatment of obesity.

Procedure: Interested persons may present data, information, or views, orally or in writing, on issues pending before the committee. Written submissions may be made to the contact person by March 6, 1998. Oral presentations from the public will be scheduled between approximately 8 a.m. and 8:30 a.m. on March 12 and 13, 1998. Time allotted for each presentation may be limited. Those desiring to make formal oral presentations should notify the contact person before March 6, 1998, and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation.

Notice of this meeting is given under the Federal Advisory Committee Act (5 U.S.C. app. 2).

Dated: February 18, 1998.

Michael A. Friedman,

Deputy Commissioner for Operations.

[FR Doc. 98–4529 Filed 2–20–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97N–0260]

Agency Information Collection Activities; Announcement of OMB Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a collection of information entitled ''Customer/Partner Satisfaction Surveys'' has been approved by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA).

FOR FURTHER INFORMATION CONTACT: Mark L. Pincus, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1471.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 2, 1997 (62 FR 63721), the agency announced that the proposed information collection had been submitted to OMB for review and clearance under section 3507 of the PRA (44 U.S.C. 3507). An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. OMB has now approved the information collection and has assigned OMB control number 0910–0360. The approval expires on January 31, 1999.

Dated: February 13, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 98–4374 Filed 2–20–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of Inspector General

Publication of the OIG Compliance Program Guidance for Hospitals

AGENCY: Office of Inspector General (OIG), HHS.

ACTION: Notice.

SUMMARY: This **Federal Register** notice sets forth the recently issued compliance program guidance for hospitals developed by the Office of Inspector General (OIG) in cooperation with, and with input from, several provider groups and industry representatives. Many providers and provider organizations have expressed an interest in better protecting their operations from fraud and abuse through the adoption of voluntary compliance programs. The first compliance guidance, addressing clinical laboratories, was prepared by the OIG and published in the **Federal Register** on March 3, 1997. We believe the development of this second program guidance, for hospitals, will continue as a positive step towards promoting a higher level of ethical and lawful conduct throughout the health care industry.

FOR FURTHER INFORMATION CONTACT: Stephen Davis, Office of Counsel to the Inspector General, (202) 619–0070.

SUPPLEMENTARY INFORMATION: The creation of compliance program guidances has become a major initiative of the OIG in its efforts to engage the private health care community in combating fraud and abuse. In developing these compliance guidances, the OIG has agreed to work closely with the Health Care Financing Administration, the Department of Justice and various sectors of the health care industry. The first of these compliance guidances focused on clinical laboratories, and was intended to provide clear guidance to those segments of the health care industry that were interested in reducing fraud and abuse within their organizations. The compliance guidance was reprinted in an OIG **Federal Register** notice published on March 3, 1997 (62 FR 9435). This second compliance program guidance developed by the OIG continues to build upon the basic elements contained in our initial compliance guidance, and encompasses principles that are applicable to hospitals as well as a wider variety of organizations that provide health care services to beneficiaries of Medicare, Medicaid and all other Federal health care programs.

Like the previously-issued compliance program guidance for clinical laboratories and future compliance program guidances, adoption of the hospital compliance program guidance set forth below will be voluntary. Future compliance program guidances to be developed will be similarly structured and based on substantive policy recommendations, the elements of the Federal Sentencing Guidelines, and applicable statutes, regulations and Federal health care program requirements.

A reprint of the OIG compliance program guidance follows.

Compliance Program Guidance for Hospitals

I. Introduction

The Office of Inspector General (OIG) of the Department of Health and Human Services (HHS) continues in its efforts to promote voluntarily developed and implemented compliance programs for the health care industry. The following compliance program guidance is intended to assist hospitals and their agents and subproviders (referred to collectively in this document as ''hospitals'') develop effective internal controls that promote adherence to applicable Federal and State law, and the program requirements of Federal, State and private health plans. The adoption and implementation of voluntary compliance programs significantly advance the prevention of fraud, abuse and waste in these health care plans while at the same time furthering the fundamental mission of