DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005N–0393]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Investigational New Drug Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by March 20, 2006.

ADDRESSES: OMB is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: Karen Nelson, Office of Management Programs (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1482.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Investigational New Drug Regulations—(OMB Control Number 0910–0014)—Extension

FDA is requesting OMB approval for the reporting and recordkeeping requirements contained in the FDA regulation ''Investigational New Drug Application'' in part 312 (21 CFR part 312). This regulation implements provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i)) to issue regulations under which the clinical investigation of the safety and effectiveness of unapproved new drugs and biological products can be conducted.

FDA is charged with implementing statutory requirements that drug products marketed in the United States be shown to be safe and effective, properly manufactured, and properly labeled for their intended uses. Section 505(a) of the act provides that a new drug may not be introduced or delivered for introduction into interstate commerce in the United States unless FDA has previously approved a new drug application (NDA). FDA approves an NDA only if the sponsor of the application first demonstrates that the drug is safe and effective for the conditions prescribed, recommended, or suggested in the product's labeling. Proof must consist, in part, of adequate and well-controlled studies, including studies in humans, that are conducted by qualified experts. The IND regulations establish reporting requirements that include an initial application as well as amendments to that application, reports on significant revisions of clinical investigation plans, and information on a drug's safety or effectiveness. In addition, the sponsor is required to give FDA an annual summary of the previous year's clinical experience. Submissions are reviewed by medical officers and other agency scientific reviewers assigned responsibility for overseeing the specific study. The IND regulations also contain recordkeeping requirements that pertain to the responsibilities of sponsors and investigators. The detail and complexity of these requirements are dictated by the scientific procedures and human subject safeguards that must be followed in the clinical tests of investigational new drugs.

The IND information collection requirements provide the means by which FDA can do the following: (1) Monitor the safety of ongoing clinical investigations; (2) determine whether the clinical testing of a drug should be authorized; (3) ensure production of reliable data on the metabolism and pharmacological action of the drug in humans; (4) obtain timely information on adverse reactions to the drug; (5) obtain information on side effects associated with increasing doses; (6) obtain information on the drug's effectiveness; (7) ensure the design of well-controlled, scientifically valid studies; (8) obtain other information pertinent to determining whether clinical testing should be continued and information related to the protection of human subjects. Without the information provided by industry in response to the IND regulations, FDA cannot authorize or monitor the clinical investigations which must be conducted prior to authorizing the sale and general use of new drugs. These reports enable FDA to monitor a study's progress, to assure subject safety, to assure that a study will be conducted ethically, and to increase the likelihood that the sponsor will conduct studies that will be useful in determining whether the drug should be marketed and available for use in medical practice.

There are two forms that are required under part 312. The first is Form FDA–1571 ''Investigational New Drug Application.'' A person who intends to conduct a clinical investigation submits this form to FDA. It includes the following information: (1) A cover sheet containing background information on the sponsor and investigator, (2) a table of contents, (3) an introductory statement and general investigational plan, (4) an investigator's brochure describing the drug substance, (5) a protocol for each planned study, (6) chemistry, manufacturing, and control information for each investigation, (7) pharmacology and toxicology information for each investigation, and (8) previous human experience with the investigational drug.

The second form required under part 312 is Form FDA–1572 ''Investigator Statement.'' Before permitting an investigator to begin participation in an investigation, the sponsor must obtain and record this form. It includes background information on the investigator and the investigation, and a general outline of the planned investigation and the study protocol.

In the **Federal Register** of October 12, 2005 (70 FR 59350), FDA published a 60-day notice requesting public comments on the information collection provisions. No comments were received that pertained to the information collection burden estimates.

FDA is requesting OMB approval for the following reporting and recordkeeping requirements in part 312:

TABLE 1.

REPORTING REQUIREMENTS	
21 CFR Section	Requirements
312.7(d)	Applications for permission to sell an investigational new drug.

TABLE 1.—Continued

REPORTING REQUIREMENTS	
21 CFR Section	Requirements
312.10(a)	Applications for waiver of requirements under part 312. Estimates for this requirement are included under §§ 312.23 and 312.31.
312.20(c)	Applications for investigations involving an exception from informed consent under § 50.24 (21 CFR 50.24). Estimates for this requirement are included under § 312.23.
312.23	INDs (content and format).
(a)(1)	Cover sheet FDA–1571.
(a)(2)	Table of contents.
(a)(3)	Investigational plan for each planned study.
(a)(5)	Investigator's brochure.
(a)(6)	Protocols—phases 1, 2, and 3.
(a)(7)	Chemistry, manufacturing, and control information.
(a)(7)(iv)(*a*), (a)(7)(iv)(*b*), and (a)(7)(iv)(*c*)	A description of the drug substance, a list of all components, and any placebo used.
(a)(7)(iv)(*d*)	Labeling: Copies of labels and labeling to be provided each investigator.
(a)(7)(iv)(*e*)	Environmental impact analysis regarding drug manufacturing and use.
(a)(8)	Pharmacological and toxicology information.
(a)(9)	Previous human experience with the investigational drug.
(a)(10)	Additional information.
(a)(11)	Relevant information.
(f)	Identification of exception from informed consent.
312.30	Protocol amendments.
(a)	New protocol.
(b)	Change in protocol.
(c)	New investigator.
(d)	Content and format.
(e)	Frequency.
312.31	Information amendments.
(b)	Content and format. Chemistry, toxicology, or technical information.
312.32	Safety reports.
(c)(1)	Written reports to FDA and to investigators.
(c)(2)	Telephone reports to FDA for fatal or life-threatening experience.
(c)(3)	Format or frequency.
(d)	Followup submissions.
312.33	Annual reports.
(a)	Individual study information.
(b)	Summary information.
(b)(1)	Adverse experiences.
(b)(2)	Safety report summary.
(b)(3)	List of fatalities and causes of death.
(b)(4)	List of discontinuing subjects.
(b)(5)	Drug action.
(b)(6)	Preclinical studies and findings.
(b)(7)	Significant changes.
(c)	Next year general investigational plan.
(d)	Brochure revision.
(e)	Phase I protocol modifications.
(f)	Foreign marketing developments.
312.35	Treatment use of investigational new drugs.
(a)	Treatment protocol submitted by an investigational new drug sponsor.
(b)	Treatment investigational new drug application (IND) submitted by licensed practitioner.
312.36	Requests for emergency use of an investigational new drug.
312.38(b) and (c)	Notification of withdrawal of an investigational new drug.
312.42(e)	Sponsor requests that a clinical hold be removed and submits a complete response to the issues identified in the clinical hold order.
312.44(c) and (d)	Opportunity for sponsor response to FDA when an investigational new drug is terminated.
312.45(a) and (b)	Sponsor request for, or response to, inactive status determination of an investigational new drug.
312.47(b)	"End-of-Phase 2" meetings and "Pre-NDA" meetings.
312.53(c)	Investigator information. Investigator report (Form FDA–1572) and narrative; Investigator's background information; phase 1 outline of planned investigation; and phase 2 outline of study protocol; financial disclosure information.
312.54(a) and (b)	Sponsor submissions concerning investigations involving an exception from informed consent under § 50.24.

TABLE 1.—Continued

REPORTING REQUIREMENTS	
21 CFR Section	Requirements
312.55(b)	Sponsor reports to investigators on new observations, especially adverse reactions and safe use. Only ''new observations'' are estimated under this section; investigator brochures are included under § 312.23.
312.56(b), (c), and (d)	Sponsor monitoring of all clinical investigations, investigators, and drug safety; notification to FDA.
312.58(a)	Sponsor's submission of records to FDA on request.
312.64	Investigator reports to the sponsor.
(a)	Progress reports.
(b)	Safety reports
(c)	Final reports.
(d)	Financial disclosure reports.
312.66	Investigator reports to Institutional Review Board. Estimates for this requirement are included under § 312.53.
312.70(a)	Investigator disqualification; opportunity to respond to FDA.
312.83	Sponsor submission of treatment protocol. Estimates for this requirement are included under §§ 312.34 and 312.35.
312.85	Sponsors conducting phase 4 studies. Estimates for this requirement are included under § 312.23 in OMB control number 0910–0014, and §§ 314.50, 314.70, and 314.81 (21 CFR 314.50, 314.70, and 314.81) in OMB control number 0910–0001.
312.110(b)	Request to export an investigational drug.
312.120(b) and (c)(2)	Sponsor's submission to FDA for use of foreign clinical study to support an IND. Estimates for this requirement are included under §§ 312.23 and 312.30 in OMB control number 0910–0014, and §§ 314.50, 314.60, and 314.70 (21 CFR 314.60) in OMB control number 0910–0001.
312.120(c)(3)	Sponsor's report to FDA on findings of independent review committee on foreign clinical study. Estimates for this requirement are included under §§ 312.23 and 312.30 in OMB control number 0910–0014, and §§ 314.50, 314.60, and 314.70 in OMB control number 0910–0001.
312.130(d)	Request for disclosable information for investigations involving an exception from informed consent under § 50.24.

RECORDKEEPING REQUIREMENTS	
21 CFR Section	Requirements
312.52(a)	Transfer of obligations to a contract research organization.
312.57(a) and (b)	Sponsor recordkeeping.
312.59	Sponsor recordkeeping of disposition of unused supply of drugs. Estimates for this requirement are included under § 312.57.
312.62(a)	Investigator recordkeeping of disposition of drugs.
312.62(b)	Investigator recordkeeping of case histories of individuals.
312.160(a)(3)	Records maintenance: shipment of drugs for investigational use in laboratory research animals or in vitro tests.
312.160(c)	Shipper records of alternative disposition of unused drugs.

In tables 2 and 3 of this document, the estimates for ''No. of Respondents,'' ''No. of Responses per Respondent,'' and ''Total Annual Responses'' were obtained from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) reports and data management systems for submissions received in 2004 and from other sources familiar with the number of submissions received under part 312. The estimates for ''Hours per Response'' were made by CDER and CBER individuals familiar with the burden associated with these reports and from estimates received from the pharmaceutical industry.

FDA estimates the burden of this collection of information as follows:

TABLE 2.—ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN FOR HUMAN DRUGS[1]

REPORTING BURDEN					
21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
312.7(d)	9	1.4	13	24	7,488
312.23(a) through (f)	1,245	1.3	1,597	1,600	2,555,200

TABLE 2.—ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN FOR HUMAN DRUGS[1]—Continued

REPORTING BURDEN

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
312.30(a) through (e)	1,257	13.3	16,687	284	4,739,108
312.31(b)	1,116	7.4	8,298	100	829,800
312.32(c) and (d)	649	24.7	16,052	32	513,664
312.33(a) through (f)	1,821	2.5	4,516	360	1,625,760
312.35(a) and (b)	5	1.2	6	300	1,800
312.36	109	1.1	121	16	1,936
312.38(b) and (c)	536	1.3	677	28	18,965
312.42(e)	97	1.2	118	284	33,512
312.44(c) and (d)	44	1	45	16	720
312.45(a) and (b)	185	1.5	271	12	3,252
312.47(b)	215	1.7	355	160	56,800
312.53(c)	21,194	1	21,194	80	1,695,520
312.54(a) and (b)	0	0	0	48	0
312.55(b)	807,400	1	807,400	48	38,755,200
312.56(b), (c), and (d)	13	1	13	80	1,040
312.58(a)	88	3.8	340	8	2,720
312.64(a) through (d)	31,791	1	31,791	24	762,984
312.70(a)	4	1	4	40	160
312.110(b)	33	8.3	276	75	20,700
312.130(d)	5	1	5	8	40
Total reporting burden					51,626,369

RECORDKEEPING BURDEN

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Hours per Record	Total Hours
312.52(a)	335	1.5	488	2	976
312.57(a) and (b)	335	119.8	40,148	100	4,014,800
312.62(a)	20,074	1	20,074	40	802,960
312.62(b)	200,740	1	200,740	40	8,029,600
312.160(a)(3)	372	1.5	542	.5	271
312.160(c)	372	1.5	542	.5	271
Total recordkeeping burden					12,848,878
Human drugs total burden hours					64,475,247

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 3.—ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN FOR BIOLOGICS[1]

REPORTING BURDEN

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
312.7(d)	41	1.4	58	24	1,392
312.23(a) through (f) and 312.120(b), (c)(2), and (c)(3)	433	1.3	557	1,808	1,007,056
312.30(a) through (e)	590	6.8	4,014	284	1,139,976
312.31(b)	263	29.3	7,700	100	770,000
312.32(c) and (d) and 312.56(c)	294	13.7	4,042	32	129,344
312.33(a) through (f) and 312.56(c)	647	2.3	1,473	360	530,280
312.35(a) and (b)	1	1	1	300	300
312.36	6	1	6	16	96
312.38(b) and (c)	117	1.3	153	28	4,284
312.42(e)	74	1.5	108	284	30,672
312.44(c) and (d)	17	1.1	18	16	288
312.45(a) and (b)	60	1.8	107	12	1,284
312.47(b)	43	1.5	66	160	10,560
312.53(c)	348	6.6	2,303	80	184,240
312.54(a) and (b)	1	1	1	48	48
312.55(b)	138	2.5	347	48	16,656
312.56(b) and (d)	14	1.6	23	80	1,840
312.58(a)	8	1	8	8	64
312.64(a) through (d)	6,003	3.5	21,185	24	508,440
312.70(a)	6	1	6	40	240
312.110(b)	21	1	21	75	1,575
312.130(d)	1	1	1	8	8
Total reporting burden					4,338,643

RECORDKEEPING BURDEN

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
312.52(a)	139	1.4	200	2	400
312.57(a) and (b)	433	2.6	1,114	100	111,400
312.62(a)	5,570	1	5,570	40	222,800
312.62(b)	5,570	10	55,700	40	2,228,000
312.160(a)(3)	146	1.4	211	0.5	105.5
312.160(c)	146	1.4	211	0.5	105.5
Total recordkeeping burden					2,562,811
Total biologics burden hours					6,901,454

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 4.—ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN FOR HUMAN DRUGS AND BIOLOGICS[1]

Total human drugs burden hours	64,475,247
Total biologics burden hours	6,901,454
Total burden hours	71,376,701

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: February 9, 2006.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E6–2289 Filed 2–16–06; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2005E–0254]

Determination of Regulatory Review Period for Purposes of Patent Extension; ERBITUX

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for ERBITUX and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Director of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human biological product.

ADDRESSES: Submit written or electronic comments and petitions to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*.

FOR FURTHER INFORMATION CONTACT: Claudia V. Grillo, Office of Regulatory Policy (HFD–013), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 240–453–6681.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Public Law 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: A testing phase and an approval phase. For human biological products, the testing phase begins when the exemption to permit the clinical investigations of the biological product becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human biological product and continues until FDA grants permission to market the biological product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Director of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human biological product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human biological product ERBITUX (cetuximab). ERBITUX, used in combination with irinotecan, is indicated for the treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for ERBITUX (U.S. Patent No. 6,217,866) from Aventis Pharmaceuticals, and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated July 8, 2005, FDA advised the Patent and Trademark Office that this human biological product had undergone a regulatory review period and that the approval of ERBITUX represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for ERBITUX is 3,375 days. Of this time, 3,192 days occurred during the testing phase of the regulatory review period, while 183 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)) became effective*: November 18, 1994. FDA has verified the applicant's claim that the date the investigational new drug application became effective was on November 18, 1994.

2. *The date the application was initially submitted with respect to the human biological product under section 351 of the Public Health Service Act (42 U.S.C. 262)*: August 14, 2003. The applicant claims August 12, 2003, as the date the product license application (BLA) for ERBITUX (BLA 125084) was initially submitted. However, FDA records indicate that BLA 125084 was submitted on August 14, 2003.

3. *The date the application was approved*: February 12, 2004. FDA has verified the applicant's claim that BLA 125084 was approved on February 12, 2004.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several statutory limitations in its calculations of the actual period for patent extension. In its application for patent extension, this applicant seeks 391 days of patent term extension.

Anyone with knowledge that any of the dates as published is incorrect may submit to the Division of Dockets Management (see **ADDRESSES**) written comments and ask for a redetermination by April 18, 2006. Furthermore, any interested person may petition FDA for a determination regarding whether the applicant for extension acted with due diligence during the regulatory review period by August 16, 2006. To meet its burden, the petition must contain sufficient facts to merit an FDA investigation. (See H. Rept. 857, part 1, 98th Cong., 2d sess., pp. 41–42, 1984.) Petitions should be in the format specified in 21 CFR 10.30.

Comments and petitions should be submitted to the Division of Dockets Management. Three copies of any mailed information are to be submitted, except that individuals may submit one