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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

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Agency Information Collection Activities; Proposed Collection; Comment Request; General Licensing Provisions: Biologics License Application, Changes to an Approved Application, Labeling Forms FDA 356h and 2567; and Revocation and Suspension

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for public comment on the proposed collection of certain information by the agency. Under the Paperwork Reduction Act of 1995 (the PRA), Federal agencies are required to publish notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on the information collection requirements relating to the general licensing provisions regarding biologics license applications, changes to an approved application, labeling, and revocation and suspension, and the use of Forms FDA 356h and 2567.

DATES: Submit written or electronic comments on the collection of information by *[insert date 60 days after date of publication in the* **Federal Register].**

ADDRESSES: Submit electronic comments on the collection of information to: http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm. Submit written comments on the collection of information to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All documents should be identified with the docket number found in brackets in the heading of this document.

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FOR FURTHER INFORMATION CONTACT: JonnaLynn P. Capezzuto, Office of Information Resources Management (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–4659.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency request or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth, in this document.

With respect to the following collection of information, FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques when appropriate, and other forms of information technology.

General Licensing Provisions: Biologics License Application, Changes to an Approved Application, Labeling Forms FDA 356h and 2567; and Revocation and Suspension (OMB Control No. 0910–0338)—Extension

Under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262), manufacturers of biological products must submit a license application for FDA review and

approval before marketing a biological product in interstate commerce. Licenses may be issued only upon showing that the establishment and the products for which a license is desired meets standards prescribed in regulations designed to ensure the continued safety, purity, and potency of such products. All such licenses are issued, suspended, and revoked as prescribed by regulations in part 601 (21 CFR part 601). Section 601.2(a) requires a manufacturer of a biological product to submit, an application with accompanying information, including labeling information, to FDA for approval to market a product in interstate commerce. The container and package labeling requirements are provided under 21 CFR 610.60, 610.61, and 610.62. Section 601.12(a) provides the general requirements for submitting a change to an approved application. Section 601.12(b), (c), and (d) requires applicants to follow specific procedures in informing FDA of each change, established in an approved license application, in the product, production process, quality controls, equipment, facilities, or responsible personnel. The appropriate procedure depends on the potential for the change to have a substantial, moderate, minimal, or no adverse effect on the safety or effectiveness of the product. Section 601.12(e) requires applicants to submit a protocol, or change to a protocol, as a supplement requiring FDA approval before distributing the product. Section 601.12(f)(1), (f)(2), and (f)(3) requires applicants to follow specific procedures in reporting labeling changes to FDA. Section 601.12(f)(4) requires applicants to report to FDA advertising and promotional labeling and any changes. Section 601.45 requires applicants to submit to the agency for consideration, during the preapproval review period, copies of all promotional materials, including promotional labeling as well as advertisements. Section 601.27(a) requires that applications for new biological products contain data that are adequate to assess the safety and effectiveness of the biological product for the claimed indications in pediatric subpopulations, and to support dosing and administration information. Section 601.27(b) provides that an applicant may request a deferred submission of some or all assessments of safety and effectiveness required under § 601.27(a). Section 601.27(c) provides that an applicant may request a full or partial waiver of the requirements under § 601.27(a). Section 601.28 requires sponsors of licensed biological

products to submit the information in section 601.28(a), (b), and (c) to the Center for Biologics Evaluation and Research (CBER) each year, within 60 days of the anniversary date of approval of the license. Section 601.28(a) requires sponsors to submit to FDA a brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Section 601.28(b) requires sponsors to submit to FDA an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. Section 601.28(c) requires sponsors to submit to FDA a statement on the current status of any post-marketing studies in the pediatric population performed by, on or behalf of, the applicant. Sections 601.33 through 601.35 clarify the information to be submitted in an application to FDA to evaluate the safety and effectiveness of in vivo radiopharmaceuticals. In addition to §§ 601.2 and 601.12, there are other regulations in parts 640,660, and 680 (21 CFR parts 640, 660, and 680) that relate to information to be submitted in a license application or supplement for certain blood or allergenic products: §§ 640.6, 640.17, 640.21(c), 640.22(c), 640,25(c), 64056(c), 640.64(c), 640.74(a) and (b)(2), 660.51(a)(4), and 680.1(b)(2)(iii). In the table 1 of this document, the burden associated with the information collection requirements in these regulations is included in the burden estimate for §§ 601.2 and 601.12. A regulation may be listed under more than one section of § 601.12 due to the type of category under which a change to an approved application may be submitted. In addition, the burden associated with the information collection requirements in § 601.27(a) and §§ 601.33 through 601.35 is included in the burden estimate for § 601.2 since these regulations deal with information to be provided in an application. Sections 600.15(b) (21 CFR 600.15(b))and 610.53(d) require the submission of a request for an exemption or modification regarding the temperature requirements during shipment and from dating periods, respectively, for certain biological products. Section 601.25(b) requests interested persons to submit, for review and evaluation by an advisory review panel, published and unpublished data and information pertinent to a designated category of biological products that have been licensed prior

to July 1, 1972. Section 601.26(f) requests that licensees submit to FDA a written statement intended to show that studies adequate and appropriate to resolve questions raised about a biological product have been undertaken for a product if designated as requiring further study under the reclassification procedures. Section 601.5(a) requires a licensee to submit to FDA notice of its intention to discontinue manufacture of a product or all products. Section 601.6(a) requires the licensee to notify selling agents and distributors upon suspension of its license, and provide FDA with records of such notification. Section 680.1(c) requires manufacturers to update annually the list of source materials and the suppliers of the materials.

In July 1997, FDA revised Form FDA 356h "Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use" to harmonize application procedures between CBER and the Center for Drug Evaluation and Research (CDER). The application form serves primarily as a checklist for firms to gather and submit to the agency studies and data that have been completed. The checklist helps to ensure that the application is complete and contains all the necessary information, so that delays due to lack of information may be eliminated. The form provides key information to the agency for efficient handling and distribution to the appropriate staff for review. The estimated burden hours for submissions using FDA Form 356h to CDER are reported under OMB Control No. 0910-0001.

Form FDA 2567 "Transmittal of Labels" and Circulars(is used by manufacturers of licensed biological products to submit labeling (e.g., circulars, package labels, container labels, etc.) and labeling changes for FDA review and approval. The labeling information is submitted with the form for license applications, supplements, or as part of an annual report. Form FDA 2567 is also used for the transmission of advertisements and promotional labeling. Form FDA 2567 serves as an easy guide to assure that the manufacturer has provided the information required for expeditious handling of their labeling by CBER. For advertisements and promotional labeling, manufacturers of licensed biological products may submit to CBER either Form FDA 2567 or FDA 2253.' Form FDA 2253 was previously used only by drug manufacturers regulated by CDER.

In August of 1998, FDA revised and harmonized Form FDA 2253 so the form may be used to transmit specimens of promotional labeling and advertisements for biological products as well as for prescription drugs and antibiotics. The revised, harmonized form updates the information about the types of promotional materials and the codes that are used to clarify the type of advertisement or labeling submitted; clarifies the intended audience for the advertisements or promotional labeling (e.g., consumers, professionals, news services); and helps ensure that the submission is complete.

Under table 1 of this document, the number of respondents is based on the estimated annual number of manufacturers that submitted the required information to F'DA in fiscal year (FY) 2000, or the number of submissions received in FY 2000. Based on information obtained from CBER's database system, there are an estimated 350 licensed biologics manufacturers. However, not all manufacturers will have any submissions in a given year and some may have multiple submissions. The total annual responses are based on the estimated number of submissions (e.g., license applications, labeling and other supplements, protocols, advertising and promotional labeling, notifications) received annually by FDA. Based on previous estimates, the rate of submissions is not expected to change significantly in the next few years. The hours per response are based on information provided by industry and past FDA experience with the various submissions or notifications. The hours per response include the time estimated to prepare the various submissions or notifications to FDA, and, as applicable, the time required to fill out the appropriate form and collate the documentation. Additional information regarding these estimates is provided below as necessary.

Under §§ 601.12(f)(4) and 601.45, manufacturers of biological products may use either Form FDA 2567 or FDA 2253 to submit advertising and promotional labeling. In FY 2000, CBER received 4,302 submissions of advertising and promotional labeling from 117 manufacturers. FDA estimates that approximately 36 percent of those submissions were received with Form FDA 2567 resulting in an estimated 1,549 submissions by 42 manufacturers. The burden hours for the

remaining submissions received using Form FDA 2253 are reported under OMB Control No. 0910-0376.

Under §§ 600.15(b) and 610.53(d), FDA receives very few requests for an exemption or modification to the requirements, therefore, FDA has estimated one respondent per year in table 1 to account for the rare instance in which a request may be made.

Under § 601.25(b)(3), FDA estimates no burden for this regulation since all requested data and information had been submitted by 1974. Under § 601.26(f), FDA estimates no burden for this regulation since there are no products designated to require further study and none are predicted in the future. However, based on the possible reclassification of a product, the labeling for the product may need to be revised, or a manufacturer, on its own initiative, may deem it necessary for further study. As a result, any changes to product labeling would be reported under § 601.12.

Under § 601.6(a), the total annual responses is based on FDA estimates that establishments may notify an average of 20 selling agents and distributors of such suspension and provide FDA with the records of such notification. The number of respondents is based on the estimated annual number of suspensions by FDA of a biologics license.

There were also 1,585 amendments to an unapproved application or supplement and 21 resubmissions (total of 1,606 submissions) submitted in FY 2000 using Form FDA 356h.

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

TABLE 1.-ESTIMATED ANNUAL REPORTING BURDEN'

21 CFR Section*	Form FDA No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
601.2(a), 610.60, 610.61, and 610.62	2567/356h	22	3.64	80	1,600	128,000
601.12(b)(l) and (b)(3)	356h	168	4.98	837	80	66,960
601.12(c)(1) and (c)(3)	356h	119	6.63	789	50	39,450
601.12(c)(5)	356h	58	3.52	204	50	10,200
601.12(d)	356h	83	1.72	143	10	1,430
601.12(e)	356h	70	1	70	20	1,400
601.12(f)(1)	2567	37	2.08	77	40	3,080
601.12(f)(2)	2567'	45	1	45	20	900
601.12(f)(3)	2567	20	1	20	10	200
601.12(f)(4) and 601.45	2567	42	36.88	1,549	10	15,490
600.15(b)	356h	1	1	1	8	8
610.53(d)	356h	1	1	1	8	8
601.25(b)(3)	NA	0	0	0	0	0
601.26(f)	NA	0	0	0	0	0
601.27(b)	NA	5	1	5	24	120
601.27(c)	NA	3	1.33	4	8	32
601.28(a)	NA	69	1	69	8	552
601.28(b)	NA	69	1	69	24	1,656

TABLE 1 .-ESTIMATED ANNUAL REPORTING BURDEN[1]—Continued

21 CFR Section*	Form FDA No.	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
601.28(c)	NA	69	1	69	1.5	103.5
601.5(a)	NA	25	1	25	.33	8.25
601.6(a)	NA	2	21	42	.33	14
680.1 (c)	NA	10	1	10	2	20
Amendments/Resubmissions	356h	350	4.59	1,606	20	32,120
Total						301,751.75

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

[2] The reporting requirement under §§ 601.27(a), 601.33, 601.34, 601.35, and 680.1(b)(2)(iii) is included in the estimate under § 601.2(a). The reporting requirement under §§ 640.6, 640.17, 640.21(c), 640.22(c), 640.25(c), 640.56(c), 640.64(c), and 640.72(a) and (b)(2) is included in the estimate under $601.12(b). The reporting requirement under §§ 640.25(c) and 640.56(c) is also included in the estimate under § 601.12(c)(3).

Dated: 2-1-02

February 1, 2002.

Margaret M. Dotzel

Margaret M. Dotzel,
Associate Commissioner for Policy.

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