Dated: December 14, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1449]

Agency Information Collection Activities; Submission for OMB Review; Comment Request; Guidance for Industry: Changes to an Approved NDA or ANDA

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

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

DATES: Submit written comments on the collection of information by January 22, 2001.

ADDRESSES: Submit written comments on the collection of information to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Wendy Taylor, Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT: Karen L. Nelson, Office of Information Resources Management (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.

Guidance for Industry: Changes to an Approved NDA or ANDA

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (the Modernization Act) (Pubic Law 105–115) into law. Section 116 of the Modernization Act amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 506A (21 U.S.C. 356a), which describes requirements and procedures for making and reporting manufacturing changes to approved new drug applications (NDA's) and abbreviated new drug applications (ANDA's), to new and abbreviated animal drug applications, and to license applications for biological products.

The guidance is intended to assist applicants in determining how they should report changes to an approved NDA or ANDA under section 116 of the Modernization Act, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

The guidance provides recommendations to holders of approved NDA's and ANDA's who intend to make postapproval changes in accordance with section 506A of the act. The guidance covers recommended reporting categories for postapproval changes for drugs, other than specified biotechnology and specified synthetic biological products. Recommendations are provided for postapproval changes in: (1) Components and composition, (2) sites, (3) manufacturing process, (4) specification(s), (5) package, (6) labeling, and (7) miscellaneous changes.

Some of the basic elements of section 506A of the act are as follows:

A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the applicant validates the effects of the change on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug (sections 506A(a)(1) and (b) of the act). This section recognizes that additional testing, beyond testing to ensure that an approved specification is met, is required to ensure unchanged identity, strength, quality, purity, or potency as these factors may relate to the safety or effectiveness of the drug.

A drug made with a major manufacturing change may be distributed only after the applicant submits a supplemental application to FDA and the supplemental application is approved by the agency. The application is required to contain information determined to be appropriate by FDA and include the information developed by the applicant when ''validating the effects of the change'' (section 506A(c)(1) of the act).

A major manufacturing change is a manufacturing change determined by FDA to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug. Such changes include: (1) A change made in the qualitative or quantitative formulation of the drug involved or in the specifications in the approved application or license unless exempted by FDA by regulation or guidance; (2) a change determined by FDA by regulation or guidance to require completion of an appropriate clinical study demonstrating equivalence of the drug to the drug manufactured without the change; and (3) other changes determined by FDA by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug (section 506A(c)(2) of the act).

FDA may require submission of a supplemental application for drugs made with manufacturing changes that are not major (section 506A(d)(1)(B) of the act) and establish categories of manufacturing changes for which a supplemental application is required (section 506A(d)(1)(C) of the act). In such a case the applicant may begin distribution of the drug 30 days after FDA receives a supplemental application unless the agency notifies the applicant within the 30-day period that prior approval of the application is required (section 506A(d)(3)(B)(i) of the act). FDA may also designate a category of manufacturing changes that permit the applicant to begin distributing a drug made with such changes upon receipt by the agency of a supplemental application for the change (section 506A(d)(3)(B)(ii) of the act). If FDA disapproves a supplemental application, the agency may order the manufacturer to cease the distribution of drugs that have been made with the disapproved change (section 506A(d)(3)(B)(iii) of the act).

FDA may authorize applicants to distribute drugs without submitting a supplemental application (section 506A(d)(1)(A) of the act) and may establish categories of manufacturing changes that may be made without submitting a supplemental application (section 506A(d)(1)(C) of the act). The applicant is required to submit a report to FDA on such a change and the report is required to contain information the agency deems to be appropriate and information developed by the applicant when validating the effects of the change. FDA may also specify the date on which the report is to be submitted (section 506A(d)(2)(A) of the act). If during a single year an applicant makes more than one manufacturing change subject to an annual reporting requirement, FDA may authorize the applicant to submit a single report containing the required information for all the changes made during the year (annual report) (section 506A(d)(2)(B) of the act).

Section 506A of the act provides FDA with considerable flexibility to

determine the information and filing mechanism required for the agency to assess the effect of manufacturing changes in the safety and effectiveness of the product. There is a corresponding need to retain such flexibility in the guidance on section 506A of the act to ensure that the least burdensome means for reporting changes are available. FDA believes that such flexibility will allow it to be responsive to increasing knowledge of and experience with certain types of changes and help ensure the efficacy and safety of the products involved. For example, a change that may currently be considered to have a substantial potential to have an adverse effect on the safety or effectiveness of the product may, at a later date, based on new information or advances in technology, be determined to have a lesser potential to have such an adverse effect. Conversely, a change originally considered to have a minimal or moderate potential to have an adverse effect on the safety or effectiveness of the product may later, as a result of new information, be found to have an increased, substantial potential to adversely affect the product. The guidance enables the agency to respond more readily to knowledge gained from manufacturing experience, further research and data collection, and advances in technology. The guidance describes the agency's current interpretation of specific changes falling into the four filing categories. Section 506A of the act explicitly provides FDA the authority to use guidance documents to determine the type of changes that do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug product. The use of guidance documents allows FDA to more easily and quickly modify and update important information.

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

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN [1]

Federal Food, Drug, and Cosmetic Act Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
506A(c)(1) and (c)(2)					
Prior approval supplement	594	3	1,782	150	267,300
506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(i)					
Changes being made (CBE) in 30-day supplement	594	5	2,970	95	282,150
506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(ii)					
CBE supplement	486	1	486	95	46,170
506A(d)(1)(A), (d)(1)(C), (d)(2)(A), and (d)(2)(B)					
Annual report	704	10	7,040	35	246,400
Total					842,020

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

Section 506A(a)(1) and (b) of the act require the holder of an approved application to validate the effects of a manufacturing change on the identity, strength, quality, purity, or potency of the drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with the change. Under section 506A(d)(3)(A) of the act, information developed by the applicant to validate the effects of the change regarding identity, strength, quality, purity, and potency is required to be submitted to FDA as part of the supplement or annual report. Thus, no separate estimates are provided for these sections in table 1 of this document; estimates for validation requirements are included in the estimates for supplements and annual reports. The guidance does not provide recommendations on the specific information that should be developed by the applicant to validate the effect of the change on the identity, strength (e.g., assay, content uniformity); quality (e.g., physical, chemical, and biological properties); purity (e.g., impurities and degradation products); or potency (e.g., biological activity, bioavailability, and bioequivalence) of a product as they may relate to the safety or effectiveness of the product.

Section 506A(c)(1) and (c)(2) of the act set forth requirements for changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes). Under these sections of the act, a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. The applicant must obtain approval of a supplement from FDA prior to distribution of a product made using the change.

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 1,782 supplements will be submitted annually under section 506A(c)(1) and (c)(2) of the act. FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 150 hours to prepare and submit to FDA each supplement.

Section 506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(i) of the act set forth requirements for changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (moderate changes). Under these sections, a supplement must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. Distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA.

Based on data concerning the number of supplements received by the agency, FDA estimates that approximately 2,970 supplements will be submitted annually under section 506A(d)(1)(B), (d)(1)(C), and (d)(3)(B)(i) of the act. FDA estimates that approximately 594 applicants will submit such supplements, and that it will take approximately 95 hours to prepare and submit to FDA each supplement.

Under section 506A(d)(3)(B)(ii) of the act, FDA may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug upon receipt by the agency of a supplement for the change. Based on data concerning the number of

supplements received by the agency, FDA estimates that approximately 486 supplements will be submitted annually under section 506A(d)(3)(B)(ii) of the act. FDA estimates that approximately 486 applicants will submit such supplements, and that it will take approximately 95 hours to prepare and submit to FDA each supplement.

Section 506A(d)(1)(A), (d)(1)(C), (d)(2)(A), and (d)(2)(B) of the act set forth requirements for changes to be described in an annual report (minor changes). Under these sections, changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product must be documented by the applicant in the next annual report.

Based on data concerning the number of supplements and annual reports received by the agency, FDA estimates that approximately 7,040 annual reports will include documentation of certain manufacturing changes as required under section 506A(d)(1)(A), (d)(1)(C), (d)(2)(A), and (d)(2)(B) of the act. FDA estimates that approximately 704 applicants will submit such information and that it will take approximately 35 hours to prepare and submit to FDA the information for each annual report.

In the **Federal Register** of September 7, 2000 (65 FR 54279), the agency requested comments on the proposed collections of information. FDA received one comment which, disagreed with the ''hours per response'' burden. The comment estimated that it would take approximately 182 hours to prepare and submit prior approval supplements; 130 hours for changes-being effected supplements; and 50 hours for changes to be described in an annual report.

FDA has considered the comment as well as other information it has received, and it has revised the burden estimates. The estimate for preparing and submitting prior approval supplements has been increased to 150 hours, from the previous estimate of 120 hours; the estimate for changes-being-effected supplements has been increased to 95 hours, from previous estimate of 80 hours; and the estimate for changes to be described in an annual report has been increased to 35 hours, from the previous estimate of 25 hours.

The comment also recommended that FDA summarize reporting requirements in a tabular format in addition to the discussion provided in the guidance, and that flow charts should be developed to aid sponsors through the process of determining the proper reporting mechanism. The comment also stated that it would be helpful to have easy access to ''such things as inks used in CDER-approved products and GMP status.''

FDA declines to discuss these suggestions in this notice. The purpose of this notice and the September 7, 2000, notice is to obtain comments on the agency's estimates of the information collection burden that would result from the Guidance ''Changes to an Approved NDA or ANDA.'' The above comments pertain to the guidance document itself and should be directed to Docket Number 99D–0529 (see the notice announcing the availability of the guidance document that published in the **Federal Register** of November 23, 1999 (64 FR 65716).

Dated: December 14, 2000.

Margaret M. Dotzel,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[HCFA–2092–N]

Medicare Program; Deductible Amount for Medigap High Deductible Policy Options for Calendar Year 2001

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Notice.

SUMMARY: This notice announces the annual deductible amount of $1,580 for the Medicare supplemental health insurance (Medigap) high deductible policy options for 2001. High deductible policy options are those with benefit packages classified as ''F'' or ''J'' that have a high deductible feature. The deductible amount represents the annual out-of-pocket expenses (excluding premiums) that a beneficiary who chooses one of these options must pay before the policy begins paying benefits.

EFFECTIVE DATE: January 1, 2001.

FOR FURTHER INFORMATION CONTACT: Kathryn McCann, (410) 786–7623.

SUPPLEMENTARY INFORMATION:

I. Background

A. Medicare Supplemental Insurance

A Medicare supplemental, or Medigap, policy is the principal type of private health insurance that a beneficiary may purchase to cover certain costs that Medicare does not cover. The beneficiary is responsible for deductibles and coinsurance amounts for both Part A (hospital insurance) and Part B (supplementary medical insurance) of the Medicare program. In addition, Medicare generally does not cover custodial nursing home care, eyeglasses, dental care, and most outpatient prescription drugs. A beneficiary must either pay the full cost of these services, or he or she may purchase additional private health insurance to help pay these costs. Medigap policies offer coverage for some or all of the deductibles and coinsurance amounts required by Medicare. Additionally, Medigap policies may provide coverage for some services that are not covered under the Medicare program.

Section 1882 of the Social Security Act (the Act) establishes, among other things, minimum standards for Medigap policies. No Medigap policy may be issued in a State unless the policy meets one of the following criteria: (a) the Secretary has certified it as meeting Federal standards and requirements, or (b) it complies with State laws established in accordance with section 1882(b)(1) of the Act.

The Omnibus Budget Reconciliation Act of 1990 (OBRA 90) amended the Act by standardizing Medigap benefits and requiring that no more than 10 Medigap benefit packages, Plans ''A'' through ''J,'' be offered nationwide. Three States (Wisconsin, Minnesota, and Massachusetts) experimented with standardizing benefits before the enactment of Federal standards. These States were permitted to keep their alternative forms of Medigap standardization, and we refer to them as the ''waivered States.''

Plan ''A'' is the basic benefit package. It covers Medicare Part A hospital coinsurance plus coverage for 365 additional days after Medicare benefits end, over the beneficiary's lifetime, Medicare Part B coinsurance (generally 20 percent of the Medicare-approved amount) or, in the case of hospital outpatient department services under a prospective payment system, the applicable copayment, and coverage for the first 3 pints of blood per year. Medigap Plans ''B'' through ''J'' contain this basic benefit package, as well as different combinations of coverage for some or all of the following benefits:

- Medicare Part A inpatient hospital deductibles.
- Skilled-nursing facility coinsurance.
- Foreign travel health emergencies, at home recovery.
- Preventive care.