CURRENT GOOD MANUFACTURING PRACTICES

FOR FINISHED PHARMACEUTICALS

OMB CONTROL NO. 0910-0139

1. Circumstances Requiring Information Collection

OMB approval under the Paperwork Reductions Act (44 U.S.C. 35) is requested for the information requirements contained in the Food and Drug Administration (FDA) Current good Manufacturing Practice (CGMP) Regulations for Finished Pharmaceuticals (21 CFR Part 211). These regulations implement §501(a)(B) of the Food, Drug and Cosmetic Act (the act) (21 U.S.C. 351(a)(2)(B)). The act requires drug manufacturers to establish and maintain quality control procedures for manufacturing, processing, and holding drugs and drug products. FDA has determined that these information requirements are essential to meeting the agency's statutory responsibility for protecting public safety and health . FDA knows no alternative means of providing equivalent public protection.

The CGMP information requirements mandate development and maintenance of detailed records. FDA uses those records to determine whether the methods, facilities, and controls used in manufacturing, processing, packing and holding of drugs conform to current good manufacturing practices. A finished drug which does not comply with these requirements is adulterated (21 U.S.C. 351 (a)(2)(B)). A manufacturer of an adulterated drug is subject to potentially severe sanctions including product seizure and criminal penalties under 21 U.S.C. 331 and 333. A good manufacturing practice is a current method, facility, or control used in the production of drugs. These manufacturing practices are designed to ensure the safety, identity, strength, quality, and purity of drug products. Although these practices must be current in the industry, they need not be widely prevalent providing it can be shown that these practices are both feasible and valuable in assuring drug quality. FDA is requesting OMB approval for the following information collection requirements in the CGMP regulations (21 CFR Part 211):

21 CFR 211.34	Recordkeeping	Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained . Records shall be maintained stating the name, address, and qualifications of any consultants and the type

		of service they provide.
21 CFR 211.67(c)	Recordkeeping	specifies that records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§.211.180 and 211.182.
21 CFR 211.68	Recordkeeping	specifies the appropriate controls that shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.
21 CFR 211.68(a)	Recordkeeping	Specifies that records be maintained of calibration checks, inspections and when applicable, computer or related system programs for automatic, mechanical, and electronic equipment.
21 CFR 211.68(b)	Recordkeeping	States that all appropriate controls shall be exercised over all computers or related systems and control data systems to assure that changes in master production and controls records or other records are instituted only by authorized persons.
21 CFR 211.72	Recordkeeping	Specifies filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. .
21 CFR 211.80(d)	Recordkeeping	Each container or grouping of containers for components or drug product containers, or closures shall be identified with distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved/rejected).
21 CFR 211.100(b)	Recordkeeping	Written production and process control

		procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.
21 CFR 211.105(b)	Recordkeeping	Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production recorded to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification numbers or code.
21 CFR 211.122(c)	Recordkeeping	Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or rejected.
21 CFR 211.130(e)	Recordkeeping	Inspection of packaging and labeling facilities immediately before use to assure that all drug products have been removed from previous operations. Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.
21 CFR 211.132(c)	Recordkeeping	Labeling. Each retail package of an OTC drug product covered by this section, except ammonia inhalant in crushable glass ampules, aerosol products as defined in paragraph (b) of this section, or containers of compressed medical oxygen, is required to bear a statement that is prominently placed so consumers are alerted to the specific tamper-resistant feature of the package. The labeling statement is required to be so place

		that it will be unaffected if the tamper-resistant feature of the package is breached or missing. If the tamper-resistant feature chosen to meet the requirement in paragraph (b) of this section is one that uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement.
21 CFR 211.132(d)	Recordkeeping	*Specifies method of Request for exemptions from packaging and labeling requirements.* A request for an exemption by a manufacturer or packer, is required to be submitted in the form of a citizen petition under §10.30 of this chapter and should be clearly identified on the envelope as a "*Request for Exemption from Tamper-Resistant Rule."* the petition is required to contain the following: (1) the name of the drug product or, is the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class. (2) The reasons that the drug product's compliance with the tamper-resistant packaging or labeling requirements of this section is unnecessary or cannot be achieved. (3) A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration, (4) Other information justifying an exemption.
21 CFR 211.137	Recordkeeping	Specifies regulations regarding expiration dating and compliance with §201.17 of this chapter.
21 CFR 211.160(a)	Recordkeeping	General Requirements-The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures,

		or other laboratory control mechanism, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.
21 CFR 211.165(e)	Recordkeeping	The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with §211.194(a)(2).
21 CFR 211.166(c)	Recordkeeping	Specifies homeopathic drug product requirements.
21 CFR 211.173	Recordkeeping	Laboratory animals- Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.
21 CFR 211.180(e)	Recordkeeping	Written records required by this part shall be maintained so that data can be used for evaluating, at least annually, the

quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations ands shall include provisions for

a random number of batches, whether approved or unapproved or rejected and where applicable, and a review of complaints, recalls returned or salvaged drug products and investigations conducted under §211.192 for each drug product.

21 CFR 211.180(f)	Recordkeeping	Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under §§211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the regulatory actions relating to good manufacturing practices brought by the FDA.
21 CFR 211.182	Recordkeeping	Specifically explains equipment cleaning and the use log.
21 CFR 211.184	Recordkeeping	Specifies component, drug product container, closure, and labeling records.
21 CFR 186	Recordkeeping	Specifies master production and control records.
21 CFR 211.188	Recordkeeping	Specifies batch production and control records.
21 CFR 211.192	Recordkeeping	Specifies the information that must be maintained on the investigation of discrepancies found in the review of al drug production and control records by the quality control staff.
21 CFR 211.194	Recordkeeping	Explanation and description of laboratory records which must be retained.
21 CFR 211.196	Recordkeeping	Specifies the information that must be included in records on the distribution of drug.
21 CFR 211.198	Recordkeeping	Specifies and describes complaint files.
21 CFR 211.204	Recordkeeping	Specifies that records be maintained of returned and salvaged drug product and describes those procedures involved.

2. How, By Whom, and for What Purpose

The purpose of these Recordkeeping requirements is to enable a manufacturer and FDA to identify and investigate any problems that may arise with a drug product. Failure to have these records available for an investigation could prevent resolution of undesirable conditions that can seriously compromise public health. FDA is authorized to inspect these records under the mandatory inspection authority of section 704 of the act (21 U.S.C. 374) (and its enforcement section under section 301 (f) of the act 21 U.S.C. 331(f)).

3. Consideration of Information Technology

Records required by CGMP regulations are designed and maintained by drug manufacturers. Because the CGMP regulations provide great latitude on how these requirements are to be achieved, manufacturers are allowed to establish their own methods of recordkeeping. FDA accepts any recordkeeping method which meets the objectives of the 21 CFR Part 211. For example, drug manufacturing establishments may use automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, to comply with these recordkeeping requirements. Computer tapes, microfiche, or microfilm or copies may be used in lieu of hard copy records to collect, retrieve and store information.

4. Identification of Duplication

As part of the retrospective review of the CGMP regulations for finished pharmaceuticals conducted in 1983, FDA examined its other regulations affecting drug manufacturers. As a consequence, duplicate CGMP provisions appearing in 21 CFR 314 were removed in 1985. No amendments to these regulations which affect recordkeeping have been made since that time.

The information required by the CGMP regulations is not available from any other source except the manufacturer. No other government agency collects these data.

5. Small Businesses

FDA must ensure that regulated products from all manufacturers (large and small) are safe and effective -- a goal achieved through equal application of the law. It is not possible to provide exemption or reduce requirements for small businesses without seriously compromising public health objectives. In order to provide assistance to small business, FDA has a small business coordinator and seven small business field representatives who exclusively help small businesses whose products are regulated by FDA. These individuals are expressly available to deal with the special concerns of small firms. They provide information that clarifies how FDA laws and regulations apply to specific circumstances and suggest methods of meeting these requirements.

They respond to inquiries, conduct or participate in workshops and conferences, or visit plants at request to offer assistance. In addition, each Center within FDA has an appropriate small business contact person who can also help to set up workshops and conferences, provide informational materials or audio visuals, or provide speakers for professional meetings.

6. Less Frequent Information Collection

The prescribed frequency for the collection of information is based upon FDA's statutory responsibility to assure the availability of uniformly high quality drug products to the nation. FDA assures compliance with CGMP recordkeeping requirements by conducting drug establishment inspections, as authorized by section 704 (21 U.S.C. 374) of the act, to review and evaluate the adequacy of records. Drug manufacturers are, in general, scheduled for these comprehensive on-site inspections once every two years. Inspections are scheduled more frequently when there have been some compliance problems. FDA investigators are authorized to examine and to copy and verify these records in order to document evidence of deviation should an enforcement case go to litigation. It would be impossible to ensure compliance with section 501(a)(2)(B) of the act (21 U.S.C.351 (a)(2)(B)) if industry were not required to maintain these records.

7. Inconsistencies with 5 CFR 1320.6

Data collection for applications is consistent with all the requirements of section 1320.6.

8. Consultations with Persons Outside FDA

In the Federal Register of December 24, 1998 (63 FR 71291), the agency requested comments on the proposed collections of information. One comment was received from a pharmaceutical trade association. The comment said that the agency's estimates of paperwork needed to comply with the CGMP regulations were far too low. The comment based its conclusion on : (1) an informal poll of seven pharmaceutical firms; (2) the assertion that the agency had not considered the records that are required by several specific sections of the regulations; (3) the added recordkeeping attendant to agency guidances; and (4) the premise that 21 CFR Part 11 (Electronic Records; Electronic signatures) imposed costs that do not offset savings of electronic recordkeeping.

The agency has carefully considered the comment and concludes that the agency's estimates of the CGMP paperwork are reasonable and correct**.** The agency's estimates are based upon not only the ERG report, but its extensive experience with a broad spectrum of industry, including small and large firms, makers of generic and innovator drug products, and repackers. FDA believes these estimates reflect a more accurate characterization of the industry than the comment suggests. FDA's estimates are based on information received from large and small pharmaceutical firms. The numbers in the burden chart reflect an average of all firms involved in the review process**.**

With respect to the comment that FDA had not considered several sections of the regulations, the agency believes there may have been some misunderstanding on the part of commentors. In fact, all sections of the regulations were considered, including those which the commentors stated "were ignored". Part of the misunderstanding is likely due to the fact that sections the commentors considered to be "ignored" were those that contained no paperwork and therefore were not factored into the final analysis.

With respect to recordkeeping that is referenced in agency guidance documents, where a guidance document addresses recordkeeping requirements that are already codified, the guidance documents themselves create no new paperwork burdens. However, the agency acknowledges that, on occasion, the information collection contained in guidance documents is beyond the scope of the regulation. The FDA recognizes the need to assure all potentially new paperwork burdens are identified, and that public comment is sought accordingly.

Regarding electronic recordkeeping, the agency fully met its obligations under the Paperwork Reduction Act in developing and issuing part 11 and received no objections to the rule with respect to paperwork reduction. In fact, extensive discussions were held with industry throughout the development of the Rule. FDA believes that the benefits of electronic recordkeeping, especially with regard to paperwork reduction, far outweigh the costs of compliance with part 11 to ensure that the electronic records are trustworthy, reliable and compatible with FDA's mandate to protect and promote public health.

The agency engages in a continuous dialog with industry and all interested parties regarding the CGMP regulations, evolving standards, and attendant recordkeeping requirements. Formal correspondence most relevant to CGMP recordkeeping takes the form of comments to Federal Register notices, such as proposed rules. For example, 115 respondents commented on the May 3, 1996 **Federal Register** proposal to amend the CGMP regulations. These included pharmaceutical organizations, individual manufacturers, industry consultants, academia, attorneys, etc. The major respondents were:

Compressed Gas Association	Arlington, VA
PhRMA (Pharm. Research & Mfgs of America)	Washington DC
PDA (Parenteral Drug Assoc)	Bethesda, MD
NDMA (Nonprescription Drug Mfrs Assoc)	Washington, DC
CTFA (Cosmetic, Toiletry & Frag. Assoc)	Washington, DC
GPIA (Generic Pharm. Ind. Assoc)	Washington, DC
Parenteral Society	Swindon, UK
Animal Health Institute	Alexandria, VA
Pharmaceutical Research Institute	Raritan, NJ
American Association of Blood Banks	Washington, DC
National Welder's Supply Assoc.	Philadelphia, PA
Abbott Laboratories	Abbott Park, IL
GlaxoWellcome	Zebulon, NC

Geneva Pharmaceuticals, Inc.	Broomfield, CO
Ciba Geigy Corporation,	Summit, NJ
Janssen Pharmaceutical Research Foundation	Titusville, NJ
Becton Dickinson & Co	Franklin Lakes, NJ
Schering - Plough Corporation	Union, NJ
Hoffman - La Roche, Inc.	Nutley, NJ
Rhone Poulenc Rorer	Collegeville, PA
St. John's University	Jamaica, NY
University of Iowa	Iowa City, IA
Massachusetts Biotechnology Council	Cambridge, MA
Department of the Army	Tacoma, WA
American Red Cross	Washington, DC
Paul G. King, Ph.D.	Lake Hiawatha, NJ
Kemper - Masterson, Inc.	Belmont, MA
AAC Consulting Group, Inc.	Bethesda, MD
King & Spaulding	Washington, DC

The agency also participates actively in numerous seminars and conferences sponsored by industry and academia. At such gatherings agency staffers engage in informal but nontheless intensive and extensive discussions about CGMPs; recordkeeping is almost always a topic of discourse. From 1996 thru 1998 the Division of Manufacturing and Product Quality (the CDER unit having primary responsibility for the CGMP regulations) gave a total of 173 presentations to industry representatives.

9. Payment or Gifts

No payment or gift was provided to respondents.

10. Confidentiality Provisions

Certain data and information collected during an inspection of a drug manufacturing establishment for the purpose of enforcing compliance with the CGMP regulations are considered confidential and not releasable to the public. Confidentiality is maintained over trade secret or confidential, commercial or financial information under 21 CFR 20.61 and investigatory records un 21 CFR 20.64. In addition, certain subparagraphs of 21 CFR 314.430 and 514.11 provide confidentiality of information contained in NDAs, ANDAs, and NADAs.

11. Sensitive Questions

There are no recordkeeping requirements regarding sexual behavior and attitudes, religious beliefs, or any other matters which are commonly considered private or sensitive in nature.

12. Total Hour Burden to Respondents

A. Hourly Burden

The information collection requirements of the CGMP regulations have been grouped according to the major information collection subjects of the regulations.

The information collection requirements of 21 CFR 211 are charted as follows:

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

Estimated Annual Recordkeeping Burden					
21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
SOP Maintenance (See previous list of 25 SOP's)	4,184	**1**	**4,184**	**25**	**104,600**
One-time Burden(new Start-up SOP's)[2]	100	25	2,500	20	50,000
211.34	4,184	.25	1,046	.5	523
211.67©	4,184	50	209,200	.25	52,300
211.68	4,184	2	8,368	1	8,368
211.68(a)	4,184	10	41,840	.5	20,920
211.68(b)	4,184	5	20,920	.25	5,230
211.72	4,184	.25	1,046	1	1,046
211.80(d)	4,184	.25	1,046	.1	105
211.100(b)	4, 184	3	12,552	2	25,104
211.105(b)	4,184	.25	1,046	.25	262
211.122©	4,184	50	209,200	.25	52,300
211.130(e)	4,184	50	209,200	.25	52,300
211.132©	1,698	20	33,960	.5	16,980
211.132(d)	1,698	.2	340	.5	170
211.137	4,184	5	20,920	.5	10,460

Estimated Annual Recordkeeping Burden					
2111.160(a)	4,184	2	8,368	1	8,368
211.165(e)	4,184	1	4,184	1	4,184
211.166©	4,184	2	8,368	.5	4,184
211.173	1,077	1	1,077	.25	269
211.180(e)	4,184	.2	837	.25	209
211.180(f)	4,184	.2	837	1	837
211.182	4,184	2	8,368	.25	2,092
211.184	4,184	3	12,552	.5	6,276
211.186	4,184	10	41,840	2	83,680
211.188	4,184	25	104,600	2	209,200
211.192	4,184	2	8,368	1	8,368
211.194	4,184	25	104,600	.5	52,300
211.196	4,184	25	104,600	.25	26,150
211.198	4,184	5	20,920	1	20,920
211.204	4,184	10	41,840	..5	20,920
Total					848,625

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2]This is a one-time burden.

B. The information collection costs imposed on the pharmaceutical industry are as follows:

__Adjusted industry labor costs per hour in 1990 = $44.20 (corrected)

--Consumer price index in 1990 128.9
--Consumer price index in April, 1995 151.9
--Percent increase in index 18.00%
--Adjusted cost per hour for 1995 $52.156

Based a total information collection burden of 298,483 hours (see above), the total annualized cost to the industry would be $15, 567,670.00

13. Estimates of Total Annual Cost to Respondents Resulting From the Collection of

Information.

There are no significant capital costs associated with the collection of information under 21 CFR Part 211.

14. Annualized Cost to FDA

The information collection costs imposed on FDA by the CGMP regulations are as follows:

The annual cost of the information requirements is the cost of the time an investigator spends reviewing the various logs (records) to insure proper adherence to manufacturing protocol or CGMP regulations. During an inspection, this time usually amounts to about 15 minutes. However, depending on the type of record and data, the time can range from 5 to 30 minutes. The length and type of record and nature of the inspection, e.g., recall, will dictate how long the review takes. Using the 15 minutes as a typical figure, this time amounts to 1/4 of the hourly salary (22.32) of a GS-12-5 investigator, which is equal to $5.58. Incidental to this cost is the time spent by the investigator writing the report of inspection, the typist's wages, and copying.

If a report is written that refers to the inspection of the record, the time/cost of the preparation of this portion of the inspection report is as follows:

Written report (Insp.- GS 12-5) 1/4 hr. X $22.32 = $5.58
Typed report (Typist - GS-05-05) 1/4 hr. X $11.03/hr. = $2.76

Cost of conducting an inspection of records:

Actual inspection	$5.58
Report of inspection	$8.34
Adjusted incidental costs per inspection -	

transportation, travel, & supplies	$17.70
TOTAL	$31.62

The annual cost of inspecting approximately 2350 manufacturers (4,700 manufacturers inspected every two years) at $31.62 per inspection, would be $74,307.00.

15. Explanation of Change

This collection of information expired February 29, 1996, which brought the inventory to zero. However, the increase in the burden hours resulted from increases in the number of responses per respondent and an increase in the number of SOP's incorporated into the collection of information.

16. Statistical Reporting

This reporting requirement does not employ statistical methods.

17. Expiration Date on Form

The required reporting forms accurately reflect the OMB approval number.

18. Exception to Certification Statement

We are not seeking any exceptions to the certification statement listed in Item 19, "Certification for Paperwork Reduction Act Submission," of OMB Form 83-I.