Current Good Manufacturing Practices For Finished Pharmaceuticals

0910-0139

SUPPORTING STATEMENT

Terms of Clearance: In accordance with 5 CFR 1320, the information collection is approved. The agency is reminded that the type of burden (recordkeeping, reporting, third-party disclosure) should be properly entered in the ROCIS system.

A. Justification

1. Circumstances Making the Collection of Information Necessary

Under Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 351(a)(2)(B)), a drug is adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with Current Good Manufacturing Practices (CGMPs) to ensure that such drug meets the requirements of the FD&C Act as to safety, and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

The FDA has the authority under Section 701(a) of the FD&C Act (21 U.S.C. 371(a)) to issue regulations for the efficient enforcement of the FD Act regarding CGMP procedures for manufacturing, processing, and holding drugs and drug products. The CGMP regulations help ensure that drug products meet the statutory requirements for safety and have their purported or represented identity, strength, quality, and purity characteristics. The information collection requirements in the CGMP regulations provide FDA with the necessary information to perform its duty to protect public health and safety. CGMP requirements establish accountability in the manufacturing and processing of drug products, provide for meaningful FDA inspections, and enable manufacturers to improve the quality of drug products over time. The CGMP

recordkeeping requirements also serve preventive and remedial purposes and provide crucial information if it is necessary to recall a drug product.

The general requirements for recordkeeping under part 211 (21 CFR part 211) are set forth in § 211.180. Any production, control, or distribution record associated with a batch and required to be maintained in compliance with part 211 must be retained for at least one year after the expiration date of the batch and, for certain OTC drugs, three years after distribution of the batch (§ 211.180(a)). Records for all components, drug product containers, closures, and labeling are required to be maintained for at least one year after the expiration date and three years for certain OTC products (§ 211.180(b)).

All part 211 records must be readily available for authorized inspections during the retention period (§ 211.180(c)), and such records may be retained either as original records or as true copies (§ 211.180(d)). In addition, § 11.2(a) (21 CFR 11.2(a)) provides that "for records required to be maintained but not submitted to the Agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met." To the extent this electronic option is used, the burden of maintaining paper records should be substantially reduced, as should any review of such records.

In order to facilitate improvements and corrective actions, records must 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 (§ 211.180(e)). Written procedures for these evaluations are to be established and include provisions for a review of a representative number of batches and, where applicable,

records associated with the batch; provisions for a review of complaints, recalls, returned or salvaged drug products; and investigations conducted under § 211.192 for each drug product.

The specific recordkeeping requirements provided in table 1 of this document are as follows:

Section 211.34—Consultants advising on the manufacture, processing, packing, or holding of drug products must have sufficient education, training, and experience to advise on the subject for which they are retained. Records must be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Section 211.67(c)—Records must be kept of maintenance, cleaning, sanitizing, and inspection as specified in §§ 211.180 and 211.182.

Section 211.68—Appropriate controls must 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.

Section 211.68(a)—Records must be maintained of calibration checks, inspections, and computer or related system programs for automatic, mechanical, and electronic equipment.

Section 211.68(b)—All appropriate controls must be exercised over all computers or related systems and control data systems to assure that changes in master production and control records or other records are instituted only by authorized persons.

Section 211.72—Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use must not release fibers into such products.

Section 211.80(d)—Each container or grouping of containers for components or drug product containers or closures must be identified with a distinctive code for each lot in each

shipment received. This code must be used in recording the disposition of each lot. Each lot must be appropriately identified as to its status.

Section 211.100(b)—Written production and process control procedures must be followed in the execution of the various production and process control functions and must be documented at the time of performance. Any deviation from the written procedures must be recorded and justified.

Section 211.105(b)—Major equipment must be identified by a distinctive identification number or code that must be recorded in the batch production record 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 number or code.

Section 211.122(c)—Records must be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination, or testing.

Section 211.130(e)—Inspection of packaging and labeling facilities must be made immediately before use to assure that all drug products have been removed from previous operations. Inspection must also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection must be documented in the batch production records.

Section 211.132(c)—Certain retail packages of OTC drug products must bear a statement that is prominently placed so consumers are alerted to the specific tamper-evident feature of the package. The labeling statement is required to be so placed that it will be unaffected if the tamper-resistant feature of the package is breached or missing. If the tamper-evident feature

chosen is one that uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement.

Section 211.132(d)—A request for an exemption from packaging and labeling requirements by a manufacturer or packer is required to be submitted in the form of a citizen petition under 21 CFR 10.30.

Section 211.137—Requirements regarding product expiration dating and compliance with 21 CFR 201.17.

Section 211.160(a)—The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, must be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. These requirements must be followed and documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms must be recorded and justified.

Section 211.165(e)—The accuracy, sensitivity, specificity, and reproducibility of test methods employed by a firm must be established and documented. Such validation and documentation may be accomplished in accordance with § 211.194(a)(2).

Section 211.166—Stability testing program for drug products.

Section 211.173—Animals used in testing components, in-process materials, or drug products for compliance with established specifications must be maintained and controlled in a manner that assures their suitability for their intended use. They must be identified, and adequate records must be maintained showing the history of their use.

Section 211.180(e)—Written records required by part 211 must 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 must be established and followed for such evaluations and must include provisions for a representative number of batches, whether approved or unapproved or rejected, and a review of complaints, recalls, returned or salvaged drug products, and investigations conducted under § 211.192 for each drug product.

Section 211.180(f)—Procedures must 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, any recalls, reports of inspectional observations issued, or any regulatory actions relating to good manufacturing practices brought by FDA.

Section 211.182—Specifies requirements for equipment cleaning records and the use log.

Section 211.184—Specifies requirements for component, drug product container, closure, and labeling records.

Section 211.186—Specifies master production and control records requirements.

Section 211.188—Specifies batch production and control records requirement.

Section 211.192—Specifies the information that must be maintained on the investigation of discrepancies found in the review of all drug product production and control records by the quality control staff.

Section 211.194—Explains and describes laboratory records that must be retained.

Section 211.196—Specifies the information that must be included in records on the distribution of the drug.

Section 211.198—Specifies and describes the handling of all complaint files received by the applicant.

Section 211.204—Specifies that records be maintained of returned and salvaged drug products and describes the procedures involved.

Written procedures, referred to here as standard operating procedures (SOPs), are required for many Part 211 records. The current SOP requirements were initially provided in a final rule published in the Federal Register of September 29, 1978 (43 FR 45014), and are now an integral and familiar part of the drug manufacturing process. The major information collection impact of SOPs results from their creation. Thereafter, SOPs need to be periodically updated. A combined estimate for routine maintenance of SOPs is provided in table 1 of this document. The 25 SOP provisions under Part 211 in the combined maintenance estimate include:

Section 211.22(d)—Responsibilities and procedures of the quality control unit;

Section 211.56(b)—Sanitation procedures;

Section 211.56(c)—Use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents;

Section 211.67(b)—Cleaning and maintenance of equipment;

Section 211.68(a)—Proper performance of automatic, mechanical, and electronic equipment;

Section 211.80(a)—Receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers or closures;

Section 211.94(d)—Standards or specifications, methods of testing, and methods of cleaning, sterilizing, and processing to remove pyrogenic properties for drug product containers and closures;

Section 211.100(a)—Production and process control;

Section 211.110(a)—Sampling and testing of in-process materials and drug products;

Section 211.113(a)—Prevention of objectionable microorganisms in drug products not required to be sterile;

Section 211.113(b)—Prevention of microbiological contamination of drug products purporting to be sterile, including validation of any sterilization process;

Section 211.115(a)—System for reprocessing batches that do not conform to standards or specifications, to insure that reprocessed batches conform with all established standards, specifications, and characteristics;

Section 211.122(a)—Receipt, identification, storage, handling, sampling, examination and/or testing of labeling and packaging materials;

Section 211.125(f)—Control procedures for the issuance of labeling;

Section 211.130—Packaging and label operations, prevention of mix-up and cross contamination, identification and handling of filed drug product containers that are set aside and held in unlabeled condition, and identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch;

Section 211.142—Warehousing;

Section 211.150—Distribution of drug products;

Section 211.160—Laboratory controls;

Section 211.165(c)—Testing and release for distribution;

Section 211.166(a)—Stability testing;

Section 211.167—Special testing requirements;

Section 211.180(f)—Notification of responsible officials of investigations, recalls, reports of inspectional observations, and any regulatory actions relating to good manufacturing practice;

Section 211.198(a)—Written and oral complaint procedures, including quality control unit review of any complaint involving specifications failures, and serious and unexpected adverse drug experiences;

Section 211.204—Holding, testing, and reprocessing of returned drug products; and

Section 211.208—Drug product salvaging.

In addition, the following regulations in parts 610 and 680 (21 CFR Parts 610 and 680) reference certain CGMP regulations in part 211: §§ 610.12(g), 610.13(a)(2), 610.18(d), 680.2(f), and 680.3(f). In table 1 of this document, the burden associated with the information collection requirements in these regulations is included in the burden estimates under §§ 211.165, 211.167, 211.188, and 211.194, as appropriate.

2. Purpose and Use of the Information Collection

The CGMP regulations help ensure that drug products meet the statutory requirements for safety and have their purported or represented identity, strength, quality, and purity characteristics. The information collection requirements in the CGMP regulations provide FDA with the necessary information to perform its duty to protect public health and safety. CGMP requirements establish accountability in the manufacturing and processing of drug products, provide for meaningful FDA inspections, and enable manufacturers to improve the quality of drug products over time. The CGMP recordkeeping requirements also serve preventive and remedial purposes and provide crucial information if it is necessary to recall a drug product.

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 FD&C Act (21 U.S.C. 374) (and its enforcement section under section 301(f) of the FD&C Act 21 U.S.C. 331(f)).

3. Use of Improved Information Technology and Burden Reduction

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.

4. Efforts to Identify Duplication and Use of Similar Information

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. Impact on Small Businesses or Other Small Entities

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 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. Consequences of Collecting the Information Less Frequently

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 FD&C 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 FD&C Act (21 U.S.C.351 (a)(2)(B)) if industry were not required to maintain these records.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

There are no special circumstances for the collection of information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In accordance with 5 CFR 1320.8(d), FDA published a 60-day notice for public comment in the FEDERAL REGISTER of November 10, 2014 (79 FR 66724). FDA received no comments that pertained to the information collection.

The Agency also engages in a continuous dialog with industry and all interested parties regarding the CGMP regulations, evolving standards, and attendant recordkeeping requirements. The Agency also participates actively in numerous seminars and conferences sponsored by industry and academia. At such gatherings, Agency staffers engage in informal but nonetheless intensive and extensive discussions about CGMPs; recordkeeping is almost always a topic of discourse.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

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 for trade secret or confidential, commercial or financial information under 21 CFR 20.61 and investigatory records under 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. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

12 a. Annualized Hour Burden Estimate

Although most of the CGMP provisions covered in this document were created many years ago, there will be some existing firms expanding into new manufacturing areas and startup firms that will need to create SOPs. As provided in table 1 of this document, FDA is assuming that approximately 100 firms will have to create up to 25 SOPs for a total of 2,500 records, and the Agency estimates that it will take 20 hours per recordkeeper to create 25 new SOPs for a total of 50,000 hours.

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

Table 1. -- Estimated Annual Recordkeeping Burden

21 CFR Section	No. of Record-keepers	No. of Records per Record-keeper	Total Annual Records	Average Burden per Record-keeping	Total Hours
SOP Maintenance	4,360	1	4,360	25	109,000
New start-up SOPs	100	25	2500	20	50,000
211.34 Consultants	4,360	.25	1,090	.5 (30 min.)	545
211.67(c) Equipment cleaning and maintenance	4,360	50	218,000	.25 (15 min.)	54,500
211.68 Changes in master production and control records or other records	4,360	2	8,720	1	8,720
211.68(a) Automatic, mechanical, and electronic equipment	4,360	10	43,600	.5 (30 min.)	21,800

211.68(b) Computer or related systems	4,360	5	21,800	.25 (15 min.)	5,450
211.72 Filters	4,360	.25	1,090	1	1,090
211.80(d) Components and drug product containers or closures	4,360	.25	1,090	.1 (6 min.)	109
211.100(b) Production and process controls	4,360	3	13,080	2	26,160
211.105(b) Equipment identification	4,360	.25	1,090	.25 (15 min.)	273
211.122(c) Labeling and packaging material	4,360	50	218,000	.25 (15 min.)	54,500
211.130(e) Labeling and packaging facilities	4,360	50	218,000	.25 (15 min.)	54,500
211.132(c) Tamper-evident packaging	1,769	20	35,380	.5 (30 min.)	17,690
211.132(d) Tamper-evident packaging	1,769	.2	354	.5 (30 min.)	177
211.137 Expiration dating	4,360	5	21,800	.5 (30 min.)	10,900
211.160(a) Laboratory controls	4,360	2	8,720	1	8,720
211.165(e)	4,360	1	4,360	1	4,360

Test methodology					
211.166 Stability testing	4,360	2	8,720	.5 (30 min.)	4,360
211.173 Laboratory animals	1,077	1	1,077	.25 (15 min.)	269
211.180(e) Production, control, and distribution records	4,360	.2	872	.25 (15 min.)	218
211.180(f) Procedures for notification of regulatory actions	4,360	.2	872	1	872
211.182 Equipment cleaning and use log	4,360	2	8,720	.25 (15 min.)	2,180
211.184 Component, drug product container, closure, and labeling records	4,360	3	13,080	.5 (30 min.)	6,540
211.186 Master production and control records	4,360	10	43,600	2	87,200
211.188 Batch production and control records	4,360	25	109,000	2	218,000
211.192 Discrepancies in drug product production and control records	4,360	2	8,720	1	8,720
211.194 Laboratory records	4,360	25	109,000	.5 (30 min.)	54,500

211.196 Distribution records	4,360	25	109,000	.25 (15 min.)	27,250
211.198 Compliant files	4,360	5	21,800	1	21,800
211.204 Returned drug products	4,360	10	43,600	.5 (50 min.)	21,800
Total					882,203

12b. Annualized Cost Burden Estimate

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Pharmaceutical industry average wage grade for maintaining this information collection	882,203	$85.00	$74,987,255

13. Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital Costs

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

We estimate that the current number of FTEs (Full Time Equivalents) devoted to enforcement and oversight of the reporting and recordkeeping burden resulting from 21 CFR 211 is approximately 283. If each FTE equals about $275,000, the total cost burden to FDA would be $77,825,000.

15. Explanation for Program Changes or Adjustments

The change in total burden hours is the result of an adjustment in agency estimates from three years ago.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no time schedules, publications, and analysis plans.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

There is no display of the expiration date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.