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Review Article

Post-Approval Activities of ANDA: USFDA Regulation and Timeline

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Abstract

Post-approval activities are equally important throughout the lifecycle of a product. After got the approval of Abbreviated New Drug Application (ANDA) a product need to go through processes like submission of Final content of labeling, Electronic Drug Registration and Listing, Pharmacovigilance activities like ADER, FAR, PAS for any changes in the approved drug product for undisturbed and smooth commercial distribution of product.FDA have it own guidance and CFR for all these activities. Post-approval requirements for marketing applications, and requirements for the production of commercial products, are similar for products approved under either a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA)..

Keywords: Food and drug administration (FDA); Abbreviated new drug application (ANDA); Adverse drug experience reports (ADE); Field alert reports (FARs); Prior-approval supplement (PAS); Code of federal regulation (CFR); National drug code (NDC); New drug application (NDA); Changes being effected (CBE)

Introduction

Starting from early development and extending through commercial marketing of the product, prescription drug manufacturers, distributors and marketers are required to comply with regulations throughout the product lifecycle. Requirements at the pre-approval stage differ from requirements in the post-approval stage. However, both stages are focused on product safety and quality [1]. As in the clinical development phases, manufacturers of approved products are required to adhere to current Good Manufacturing Practice (CGMP) regulations, and sponsors are required to report changes that have a potential effect on the product's safety and quality to the US Food and Drug Administration (FDA) [2]. Pre-approval of ANDA is lengthy process which undergoes activities like approval for Bioequivalence report, plant inspection, CMC approval and labeling approval. First activity after got the approval letter is submission of final labeling content and electronic drug listing so that approved drug name appear in the orange book. After that manufacturer or marketing authorization holder of approved product need to follows pharmacovigilance activities like ADER, FAR. If the manufacturer or marketing authorization holder wants to change anything from its submitted information need to do these activities as per FDA's PAS guidance or CFR.

Electronic Drug Registration and Listing with Final Content of Labeling

Requirements for drug establishment registration and drug listing are set forth in section 510 of the Federal Food, Drug, and Cosmetic Act (the Act) and section 351 of the Public Health Service Act (the PHS Act), and 21 CFR Part 207. Fundamental to FDA's mission to protect the public health is the collection of this information, which is used for important activities such as postmarked surveillance for serious adverse drug reactions, inspection of drug manufacturing and processing facilities, and monitoring of drug products imported into the United States [3]. Comprehensive, accurate, and up-to-date information is critical to conducting these activities with efficiency and effectiveness.

Section 510 of the Act and 21 CFR part 207, subject to certain limited exceptions, require establishment owners and operators (registrants) upon first engaging in the manufacture, preparation, propagation, compounding, or processing of drugs, (including human drugs, veterinary drugs, and biological drug products) to register their establishments and submit listing information for all drugs in commercial distribution.

a. Registrants are also required to submit registration information for their establishments on or before December 31 of each year.

b. 1 At the time of registration, registrants must also submit required listing information.

c. Additionally, registrants are required to update listing information in June and December of each year to include information for drugs that have not been previously listed.

d. 3 Certain changes to information for previously listed drugs must also be submitted every June and December.4

Changes in the Act, resulting from the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) (FDAAA) [4], require that drug establishment registration and drug listing information be submitted electronically unless a waiver is granted.

Who Must List Drugs and What Drugs Must They List?

A. Each registrant must list each drug that it manufactures, repacks, relabels, or salvages for commercial distribution. Each domestic registrant must list each such drug regardless of whether the drug enters US market. When operations are conducted at more than one establishment, and common ownership and control exists among all the establishments, the parent, subsidiary, or Affiliate Company may submit listing information for any drug manufactured, repacked, relabeled, or salvaged at any such establishment. A drug manufactured, repacked, or relabeled for private label distribution must be listed in accordance with paragraph (c) of this section [5].

B. Registrants must provide listing information for each drug in accordance with the listing requirements described in 21 CFR parts 207 that correspond to the activity or activities they involve in for that drug.

C. For both animal and human drugs, each registrant must list each drug it manufactures, repacks, or relates for distribution under the trade name or label of a private label distributor using an NDC that includes distributor's labeler code.

D. Additionally, in the case of human drugs, each registrant must list each human drug it manufactures, repacks, or relates using an NDC that includes the registrant's own labeler code [5].

What Listing Information Must a Registrant Submit for a Drug It Manufactures?

[6] Each registrant must provide the following listing information for each drug it manufactures for commercial distribution.

A. The appropriate NDC(s), as described in §207.33, that include all package code variations. In the case of human drugs, the appropriate NDC(s) submitted under this paragraph include the registrant's labeler code. In the case of animal drugs, the appropriate NDC(s) submitted under this paragraph include the registrant's labeler code, except that when the drug is manufactured for commercial distribution under the trade name or label of a private label distributor, the appropriate NDC(s) for animal drugs include the private label distributor's labeler code;

B. Package type and volume information corresponding to the package code segment of the NDC;

C. The listed drug's established name and proprietary name, if any:

a. The name and quantity of each active pharmaceutical ingredient in the listed drug.

b. The name of each inactive ingredient along with any declarations of confidentiality associated with individual inactive ingredients.

c. The dosage form.

d. The drug's approved U.S. application number, if any.

e. The drug type (e.g., as applicable, finished vs. unfinished, human vs. animal, prescription vs. nonprescription).

f. In the case of an unfinished drug, the number assigned to the Drug Master File or Veterinary Master File, if any, that describes the manufacture of the drug.

g. For each drug that is subject to the imprinting requirements of part 206 of this chapter including products that are exempted under §206.7(b), the drug's size, shape, color, scoring, and code imprint (if any).

D. The route or routes of administration of the drug.

E. For each drug bearing an NDC:

a. The name and Unique Facility Identifier of the establishment and the type of operation performed.

b. The name and Unique Facility Identifier of every other establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

F. The schedule of the drug under section 202 of the Controlled Substances Act, if applicable.

G. Advertisements:

a. A representative sampling of advertisements for a human prescription drug.

b. If FDA requests it, for good cause, a copy of all advertisements for a human prescription drug that is not subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, including those advertisements described in §202.1(l)(1) of this chapter.

Such advertisements must be submitted within 30 calendar days after FDA's request.

H. Provide the following labeling(as applicable)for drugs bearing the NDC(s) except those drugs manufactured exclusively for private label distribution and not distributed under the registrant's own name and label.

a. Human prescription drugs. All current labeling content except that only one representative container or carton label need to be submitted where differences exist only in the quantity of contents statement or the bar code. This labeling submission must include the content of labeling, as defined in 21 CFR parts 207.

b. Human nonprescription drugs. (A) All current labeling, except that only one representative container or carton label need to be submitted where differences exist only in the quantity of contents statement or the bar code For each human nonprescription drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act. This labeling submission must include the content of labeling, as defined in 21 CFR parts 207.

I. For each human nonprescription drug not subject to section 505 of the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, the current label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement or the bar code), the package insert (if any), and a representative sampling of any other labeling. This labeling submission must include the content of labeling as defined in section §207.1(b).

a. Animal drugs. (A) For each animal drug that is subject to section 512 of the Federal Food, Drug, and Cosmetic Act, which includes, but is not limited to, new animal drugs that have been approved, conditionally approved, or indexed under sections 512, 571, or 572 of the Federal Food, Drug, and Cosmetic Act, a copy of all current labeling (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement), including the content of labeling as defined in 21 CFR parts 207.

J. For all other animal drugs, a copy of the current label (except that only one representative container or carton label need be submitted where differences exist only in the quantity of contents statement), the package insert, the content of labeling as defined in 21 CFR parts 207, and a representative sampling of any other labeling.

a. All other listed drugs. For all other listed drugs, including unfinished drugs, the label (if any), except that only one representative label need be submitted where differences exist only in the quantity of contents statement.

K. Listing submissions described in 21 CFR §207.41(c) (2) for human drugs manufactured for private label distribution must include all information specified in 21 CFR §207.49(a) (2) through (14) a

a. The appropriate NDC(s) (as described in 21 CFR §207.33) that include the private label distributor's labeler code and all package code variations.

b. The name, mailing address, telephone number, and email address of the private label distributor.

c. For drugs bearing the NDC(s) reported under paragraph (a) (16) (i) of this section, labeling as described in paragraph.

d. Of this section that accompanies the private label distributor's product.

e. Additionally, each registrant is requested to provide the following information for each human drug it manufactures for commercial distribution

f. The drug's over-the-counter monograph reference.

g. The date on which the drug was or will be introduced into commercial distribution.

Timeline

Submission of initial registration of an establishment and drug listing information

[7] For each drug being manufactured, repacked, relabeled, or salvaged for commercial distribution at an establishment at the time of initial registration, drug listing information must be submitted no later than 3 calendar days after the initial registration of the establishment.

Submission of final SPL after approval?

[8] The final SPL should be submitted preferably within 14 calendar days after approval.

Field Alert Reports

Field Alert report is report which required to be filed when significant problem is identified through complaint and / or internal investigation and / or internal testing and has substantial potential to pose health hazard to the public. An issue arising from a product quality complaint, an inquiry or request for information from any of the below concerns may lead to the issuance of a Field Alert Report (FAR):

a. FDA

b. A patient

c. A health Care Professional (HCP)

d. A medical Care Organization (MCO)

e. Notification from a Distributor/Manufacturer/Packaging/ laboratory-testing contractor

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Reporting Field Alert Events

The purpose of Field Alert Reports (FARs), required to quickly identify drug products that pose potential safety threats. Holders of approved NDAs or ANDAs are required to submit FARs within three days of becoming aware of any significant problem with a distributed drug product. FARs may be communicated to the district FDA office by telephone or other rapid means, but must be followed by a written report. 21 CFR 314.81(b) requires the following information be reported in an FAR:

a. Incidents causing the drug product or its labeling to be mistaken for or applied to another article

b. Bacterial contamination

c. Significant chemical, physical or other change, deterioration in the distributed drug product

d. Failure of one or more distributed drug product batches to meet the specifications established in the approved application

Post Marketing Surveillance of Drugs and Biologics

Post marketing surveillance is the systematic collection, analysis, interpretation and dissemination of health-related data to improve public health and reduce morbidity and mortality. FDA requires manufacturers, packagers and distributors of marketed prescription and nonprescription drug products to establish and maintain records and make reports to the agency of all serious, unexpected adverse drug experiences associated with the use of their drug products. Reporting by healthcare professionals outside industry is voluntary.

Definitions

The following definitions apply to post marketing adverse drug experience reporting:

a. [9] Adverse drug experience-An adverse drug experience is any adverse event associated with the use of a drug, whether or not considered drug related, including:

b. An adverse event occurring in the course of the drug product's use in professional practice

c. An adverse event occurring from drug overdose, whether accidental or intentional

d. An adverse event occurring from drug abuse

e. An adverse event occurring from drug withdrawal

f. Any failure of expected pharmacological action

g. Associated with the use of the drug-There is a reasonable possibility the experience may have been caused by the drug.

h. Disability-An adverse event resulting in a substantial disruption of a person's ability to conduct normal life functions.

i. FDA Adverse Event Reporting System (FAERS)-A computerized information database designed to support FDA's post marketing safety surveillance program for drug and no vaccine biological products.

j. Individual Case Safety Report (ICSR)-A description of an adverse experience related to an individual patient or subject.

k. Life-threatening adverse drug experience-Any adverse drug experience placing the patient, in the view of the initial reporter, at immediate risk of death from the adverse drug experience as it occurred, i.e., does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

l. Serious adverse drug experience-Any adverse drug experience occurring at any dose resulting in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions not resulting in inpatient hospitalization or the development of drug dependency or drug abuse.

m. Unexpected adverse drug experience-An unexpected adverse drug experience is any adverse drug experience not listed in the drug product's current labeling. This includes events that may be symptomatically and path physiologically related to an event listed in the labeling but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral (of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been observed previously (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmaceutical product's pharmacological properties.

Adverse Drug Experience Reports (ADE)

Post marketing reporting requirements for ADEs are outlined in 21 CFR 314.80. These regulations require the holder of an approved application under 21 CFR 314.50 or an effective 505 (b) (2) to review all reports of adverse experience received regardless of the source (foreign or domestic) promptly. Potential ADE information sources cited in 21 CFR 314.80 include:

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a. Information derived from commercial marketing experience

b. Post marketing clinical investigations

c. Post marketing epidemiological/surveillance studies

d. Reports in scientific literature

e. Unpublished scientific papers

The applicant is required to submit the following ADE reports to FDA within the specified timeframes:

a. Post marketing 15-Day Alert Reports-A sponsor must report all ADEs (foreign or domestic) that are both serious and unexpected to FDA within 15 days of receipt of the information. The applicant must investigate all ADE reports promptly and submit any additional information obtained during the investigation within 15 days of receipt as follow-up reports or as requested by FDA.

b. Periodic Adverse Drug Experience Reports (PADER)- For the first three years following a drug's approval, a sponsor shall submit PADERs on a quarterly basis. Unless otherwise requested by FDA, after three years, the sponsor shall submit a PADER at annual intervals. The PADER should contain:

c. A narrative summary and analysis of the report's information, including all ADE information obtained during the reporting period and analysis of 15-Day Alert Reports submitted during the reporting interval.

d. Any Form FDA 3500A (Med Watch) for an ADE not submitted as a 15-Day Alert Report.

e. Any actions taken during the reporting period due to ADEs (e.g., labeling changes or additional studies initiated).

To encourage healthcare professionals to collect, evaluate and report serious ADEs, FDA developed the Med Watch educational and publicity program in 1993. Sponsors, manufacturers, distributors and user facilities use Med Watch Form 3500A for mandatory reporting of both adverse events and problems with human drugs and other FDA-regulated products. Healthcare professionals, consumers and patients may use Med Watch Form 3500 for spontaneous ADE reporting to the sponsor or directly to FDA. Foreign reportable ADEs also may be submitted on forms developed by the Council for International Organizations of Medical Sciences (CIOMS). FDA tracks adverse drug reaction reports by entering all safety reports for approved drugs and therapeutic biological products into the FDA Adverse Event Reporting System (FAERS) database, which uses standardized international terminology from the Medical Dictionary for Regulatory Activities (Med DRA). FDA uses FAERS to facilitate post-marketing drug surveillance and compliance activities. The FAERS goal is to improve the public health by providing the best available tools for storing and analyzing safety data and reports.

Post Approval Changes

[10-12] FDA defines 4 reporting categories of the post approval changes which are listed below.

A. Major Change

B. Moderate Change- It is categorized into 2 types-

a. The change requiring the submission of Supplement-Changes Being Effected in 30 Days

b. The change requiring the submission of Supplement-Changes Being Effected

C. Minor Change

Major Change

a. A major change is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or efficacy of the drug product.

b. A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called and should be clearly labeled as Prior approval supplement.

c. An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons like drug shortage or in case if there is a delay would impose an extraordinary hardship on the applicant.

Moderate Change

A moderate change is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

The moderate change is categorized into 2 types based on the type of supplement being filed-

a. Supplement-Changes being affected in 30Days (CBE-30supplement): A CBE-30 supplement involves certain moderate changes that require the submission of the supplement to FDA at least 30 days before the distribution of the drug product made using the change.

b. Supplement- Changes Being Effected (CBE-0 supplement): A CBE-0 supplement involves certain moderate changes that allow distribution to occur as soon as FDA receives the supplement.

Minor Change

A minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or efficacy of the drug product. The applicant must describe minor changes in its next Annual Report.

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Annual Reports

Holders of approved applications are required to submit Annual Reports to FDA. The Annual Report is sent to the division responsible for the application's review. The reporting period is defined as one full year from the anniversary date of the application's approval; the Annual Report must be submitted within 60days of this anniversary date. The content of an Annual Report is outlined below.

FDA Forms and Cover Letter

The Annual Report should include a cover letter, which indicates product name, application number, reporting period and any additional information the sponsor may wish to bring to the agency's attention. Additionally, a completed Form FDA 2252 (Transmittal of Annual Reports for Drugs and Biologics for Human Use) is to be submitted with the Annual Report [13].

Summary of Significant New Information

a. [14] Summary of significant new information possibly affecting the drug product's safety, effectiveness or labeling, and a description of actions the sponsor has taken or intends to take as a result of this new information

b. Indication of whether labeling supplements for pediatric use have been submitted, and whether new studies in the pediatric population have been initiated to support appropriate labeling for the pediatric population.

Distribution Data

a. [15] Quantity of product distributed under the approved application including amounts provided to distributors

b. (The distribution data must include the National Drug Code (NDC) number, total number of dosage units of each strength or potency)

c. Quantities distributed for domestic and foreign use.

Labeling

a. [16]current professional labeling, patient brochures or package inserts and representative samples of package labels

b. content of labeling required under 21 CFR 201.100(d)(3) (i.e., the package insert or professional labeling), including all text, tables and figures provided in electronic format

c. a summary of any labeling changes made since the last report, listed by date in the order in which they were implemented or, if no changes, a statement of that fact

Chemistry, Manufacturing and Controls

a. [17] reports of experiences, investigations, studies or tests involving physical, chemical, or any other properties of the drug

b. CMC index: a current list of approved CMC information, which is intended to aid the agency's review of the Annual Report (i.e., list of approved analytical methods, specifications, manufacturing sites, etc.) The index should include the type and date of each change to each component, the type of submission used to report the change (original, supplement, or Annual Report), and the date the change was reported and approved, if an application was submitted.

c. a complete description of CMC changes not requiring a supplemental application under 21 CFR 314.70(b) (i.e., "Annual Reportable" changes)

d. stability data obtained during the reporting period

Nonclinical Laboratory Studies

[18] The application holder should provide copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies or in vitro studies. Nonclinical laboratory study reports should include all studies conducted by, or otherwise obtained by, the application holder.

Clinical Data

a. [19] published clinical trials (or abstracts) of the drug, including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutical, pharmacokinetic and clinical pharmacology studies; and reports of clinical experience related to safety, conducted by the sponsor or found in the public domain

b. summaries of completed unpublished clinical trials or available prepublication manuscripts conducted by the sponsor or found in the public domain

c. Analysis of available safety and efficacy data in the pediatric population and changes in labeling based on this information (This also should include an assessment of data needed to ensure appropriate labeling for the pediatric population.)

Status Reports of Post marketing Study Commitments

[20] Status report on each post marketing requirement (PMR) or post marketing commitment (PMC) concerning clinical safety, clinical efficacy, clinical pharmacology and nonclinical toxicology.

25. Status of Other Post marketing Studies

[21]Status report of any post marketing study not included in the PMR/PMC section above; primarily relates to CMC post marketing studies and product stability studies

Log of Outstanding Regulatory Business

[22] At the sponsor's discretion, the Annual Report also may include a listing of any open regulatory business with FDA concerning the application (e.g., a list of unanswered correspondence between the sponsor and FDA, or vice-versa) Figure 1. FDA will review each submitted supplement and Annual Report.If FDA determines

a supplement or Annual Report is incomplete, the sponsor cannot distribute the product manufactured until it addresses the deficiency as required by the agency. If the product with the proposed change is in commercial distribution already (e.g., the product was distributed after a Changes Being Effected (CBE) supplement was submitted), and FDA believes the supplement is deficient, the agency may order the manufacturer to cease product distribution until the supplement is amended [23].

Conclusion

As FDA publishes all the activities publicly, if anything goes wrong it will hamper the business growth and goodwill of company. So every manufacturer or marketing authorization holder always needs to comply with 21 CFR. For the entire commercially distributed and approved drug product below are the summaries need to follow not only for the business purpose but also the reputation of the company.

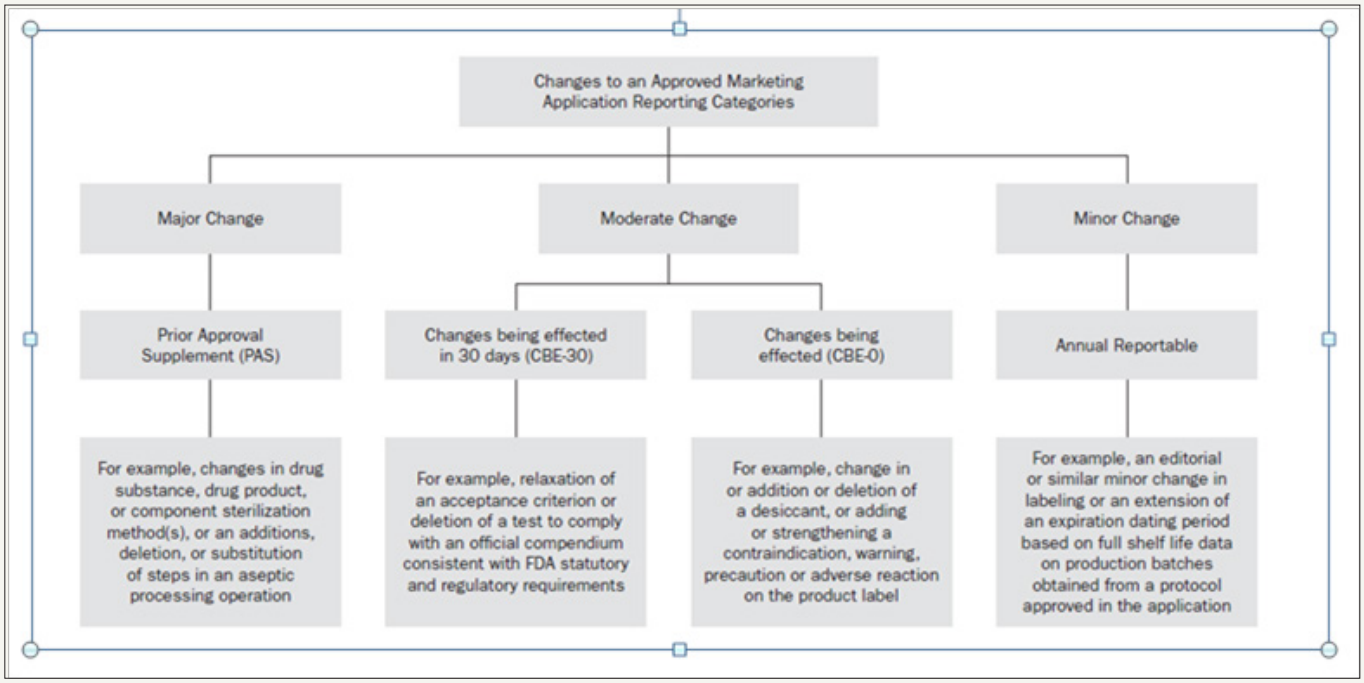

Figure 1: Summary of reporting categories for post-approval changes.

a. Post marketing requirements and commitments are studies and clinical trials conducted after a product is approved. The purpose of these studies is to collect additional safety, efficacy or optimal use data on the approved product.

b. Sponsors of approved marketing applications are required to report almost all changes to FDA under the FD&C Act. The agency has provided numerous guidance documents to aid application holders in determining the appropriate reporting category for post-approval changes to components and composition, manufacturing sites, analytical testing sites, manufacturing process, specifications, container closure systems and labeling. These guidance documents also provide advice on handling multiple related changes.

c. Post-approval changes to CMC or labeling sections of an application must be assessed for the appropriate reporting category (major, moderate or minor) and submitted in a supplement corresponding to that level of change (i.e., PAS, CBE-30, CBE-0) or Annual Report.

d. Sponsors of approved marketing applications are required to review ADE information obtained from all potential sources. They are required to report post marketing safety information to FDA in 15-Day Alert Reports and periodic ADE reports.

e. Sponsors of approved applications are required to submit an Annual Report. Each copy of the report must be accompanied by a completed Form FDA 2252 (Transmittal of Periodic Reports for Drugs for Human Use). The period covered in the report is defined as one full year from the approval anniversary date of the preceding year. The report should include a summary; distribution data; status of labeling; chemistry, manufacturing and controls information; nonclinical laboratory studies; clinical data; status of post marketing study requirements and commitments; status of other post marketing studies; and a log of outstanding regulatory business.

f. Manufacturers are required to register drug establishments on an annual basis and provide a current drug product list to FDA on a semi-annual basis. Drug Establishment registration must be submitted in electronic format.

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16. 21 CFR 314.81(b) (2) (iii).
17. 21 CFR 314.81(b) (2) (iv).
18. 21 CFR 314.81(b) (2) (v).
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