JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue

JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)

An International Scholarly Open Access, Peer-reviewed, Refereed Journal

CHANGES TO AN APPROVED NDA AND ANDA

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ABSTRACT

NDA is a type of application in which a pharmaceutical manufacturer or its agent requests permission from the U.S. Food and Drug Administration (FDA) for a license to market a drug for one or more specified indications. In addition to a chemical and pharmacologic description of the drug, an NDA must show the results of clinical trials conducted with respect to the indication for which a license is requested. The present thesis mainly discusses about the changes to approved nda and and a. On November 21, 1997, the Food & Drug Modernization Act (the Modernization Act) was enacted by Congress. Section 116 of the Modernization Act amended the Federal Food, Drug, and Cosmetic (FD&C) Act to add section 506A. This section outlines the requirements for making and reporting manufacturing changes to approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs), as well as the requirements for distributing a drug product made with these changes. In order to comply with section 506A, the FDA then revised its regulations regarding supplements and other changes to an approved application. If the holder of an NDA or ANDA is planning to make post-approval changes, they first need to specify the types of changes they'll make which fall under one of three categories: major, moderate, or minor.

INTRODUCTION

New Drug Application: (NDA) is a type of application in which a pharmaceutical manufacturer or its agent requests permission from the U.S. Food and Drug Administration (FDA) for a license to market a drug for one or more specified indications.

In addition to a chemical and pharmacologic description of the drug, an NDA must show the results of clinical trials conducted with respect to the indication for which a license is requested.

Whereas a NDA is used for drugs subject to the drug approval provisions of the United States Federal Food, Drug, and Cosmetic (FD&C) Act, a biologics license application (BLA) is required for biological products (biologics) subject to licensure under the Public Health Service (PHS) Act.

The NDA review includes: Medical Review(s) Chemistry Review(s) Environmental Assessment Pharmacology Review(s) Statistical Review(s) Microbiology Review(s)
Clinical Pharmacology/Biopharmaceutics Review(s) Risk Assessment and Risk Mitigation Review(s)

The purpose of a NDA is to provide enough information to permit the FDA to reach the following key decisions

1. Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
2. Whether the drug's proposed labeling (package insert) is appropriate and what it should contain.
3. Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

A pharmaceutical company seeking FDA approval to sell a new prescription drug must complete a five-step process:

Discovery/concept,
Preclinical research,
Clinical research,
FDA review and
FDA post-market safety monitoring.

Developing New Drugs:

American consumers benefit from having access to the safest and most advanced pharmaceutical system in the world. The main consumer watchdog in this system is FDA's Center for Drug Evaluation and Research (CDER).

The center's best-known job is to evaluate new drugs before they can be sold. CDER's evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. The center ensures that drugs, both brand - name and generic, work correctly and that their health benefits outweigh their known risks.

Drug companies seeking to sell a drug in the United States must first test it. The company then sends CDER the evidence from these tests to prove the drug is safe and effective for its intended use. A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the company's data and proposed labeling.

If this independent and unbiased review establishes that a drug's health benefits outweigh its known risks, the drug is approved for sale. The center doesn't actually test drugs itself, although it does conduct limited research in the areas of drug quality, safety, and effectiveness standards.

Before a drug can be tested in people, the drug company or sponsor performs laboratory and animal tests to discover how the drug works and whether it's likely to be safe and work well in humans. Next, a series of tests in people is begun to determine whether the drug is safe when used to treat a disease and whether it provides a real health benefit.

For more information about the drug development and approval process, see How Drugs Are Developed and Approved.

FDA Approval: FDA approval of a drug means that data on the drug’s effects have been reviewed by CDER, and the drug is determined to provide benefits that outweigh its known and potential risks for the intended population. The drug approval process takes place within a structured framework that includes:

Analysis of the target condition and available treatments—FDA reviewers analyze the condition or illness for which the drug is intended and evaluate the current treatment landscape, which provide the context for weighing the drug’s risks and benefits.

For example, a drug intended to treat patients with a life-threatening disease for which no other therapy exists may be considered to have benefits that outweigh the risks even if those risks would be considered unacceptable for a condition that is not life threatening.

Assessment of benefits and risks from clinical data—FDA reviewers evaluate clinical benefit and risk information submitted by the drug maker, taking into account any uncertainties that may result from imperfect or incomplete data. Generally, the agency expects that the drug maker will submit results from two

well-designed clinical trials, to be sure that the findings from the first trial are not the result of chance or bias.

In certain cases, especially if the disease is rare and multiple trials may not be feasible, convincing evidence from one clinical trial may be enough. Evidence that the drug will benefit the target population should outweigh any risks and uncertainties.

Strategies for managing risks—All drugs have risks. Risk management strategies include an FDA-approved drug label, which clearly describes the drug's benefits and risks, and how the risks can be detected and managed. Sometimes, more effort is needed to manage risks. In these cases, a drug maker may need to implement a Risk Management and Mitigation Strategy (REMS).

Although many of the FDA's risk-benefit assessments and decisions are straightforward, sometimes the benefits and risks are uncertain and may be difficult to interpret or predict. The agency and the drug maker may reach different conclusions after analyzing the same data, or there may be differences of opinion among members of the FDA's review team. As a science-led organization, FDA uses the best scientific and technological information available to make decisions through a deliberative process.

Accelerated Approval

In some cases, the approval of a new drug is expedited. Accelerated Approval can be applied to promising therapies that treat a serious or life-threatening condition and provide therapeutic benefit over available therapies. This approach allows for the approval of a drug that demonstrates an effect on a "surrogate endpoint" that is reasonably likely to predict clinical benefit, or on a clinical endpoint that occurs earlier but may not be as robust as the standard endpoint used for approval. This approval pathway is especially useful when the drug is meant to treat a disease whose course is long, and an extended period of time is needed to measure its effect.

After the drug enters the market, the drug maker is required to conduct post -marketing clinical trials to verify and describe the drug's benefit. If further trials fail to verify the predicted clinical benefit, FDA may withdraw approval.

Since the Accelerated Approval pathway was established in 1992, many drugs that treat life-threatening diseases have successfully been brought to market this way and have made a significant impact on disease course. For example, many antiretroviral drugs used to treat HIV/AIDS entered the market via accelerated approval, and subsequently altered the treatment paradigm. A number of targeted cancer-fighting drugs also have come onto the market through this pathway.

More information on Accelerated Approval is here. Drug Development Designations. The agency also employs several approaches to encourage the development of certain drugs, especially drugs that may represent the first available treatment for an illness, or ones that have a significant benefit over existing drugs. These approaches, or designations, are meant to address specific needs, and a new drug application may receive more than one designation, if applicable. Each designation helps ensure that therapies for serious

conditions are made available to patients as soon as reviewers can conclude that their benefits justify their risks.

Fast Track is a process designed to facilitate the development and advance the review of drugs that treat serious conditions, and fill an unmet medical need, based on promising animal or human data. Fast tracking can get important new drugs to the patient earlier.

The drug company must request the Fast Track process. More information about the Fast Track process is here.

Breakthrough Therapy designation expedites the development and review of drugs that are intended to treat a serious condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy. A drug with Breakthrough Therapy designation is also eligible for the Fast Track process. The drug company must request a Breakthrough Therapy designation. More information about Breakthrough Therapy designation is here.

Priority Review means that FDA aims to take action on an application within six months, compared to 10 months under standard review. A Priority Review designation directs attention and resources to evaluate drugs that would significantly improve the treatment, diagnosis, or prevention of serious conditions. More information about Priority Review is here.

Abbreviated New Drug Application: (ANDA) is a written request to the U.S. Food and Drug Administration (FDA) to manufacture and market a generic drug in the United States.1 Abbreviated New Drug Applications are “abbreviated” since they do not require the applicant to conduct clinical trials and require less information than a New Drug Application. The Food and Drug Administration (FDA) is responsible for advancing the public health by helping to speed innovations that make medicines safer and more effective and by helping the public get the accurate, science-based information it needs to use medicines to maintain and improve public health.

This publication emphasizes quality system approaches to the development and availability of new drug information presented in the proposed labeling of the product. In 2004, the FDA provided a guidance document for innovations, challenges, and solutions for new drug products that examine the critical path needed to bring therapeutic products to completion, and how the FDA can collaborate in the process, from laboratory to production to end use, to make medical breakthroughs available to those in need as quickly as possible.

The Food and Drug Administration's (FDA) **New Drug Application** (**NDA**) is the vehicle in the United States through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing.[1][2] Some 30% or less of initial drug candidates proceed through the entire multi-year process of drug development, concluding with an approved NDA, if successful.

The goals of the NDA are to provide enough information to permit FDA reviewers to establish the complete history of the candidate drug.

- Among facts needed for the application are:
- Patent and manufacturing information
- Drug safety and specific effectiveness for its proposed use(s) when used as directed
- Reports on the design, compliance, and conclusions of completed clinical trials by the Institutional Review Board
- Drug susceptibility to abuse
- Proposed labeling (package insert) and directions for use

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance.

NDA Requirements	**ANDA Requirements**
Labelling	Labelling
Toxicology	Toxicology
Pharmacology	Pharmacology
Manufacturing	Manufacturing
Controls	Controls
Chemistry	Chemistry
Animal Studies	Bioequivalence
Clinical Studies	
Bioavailability	

REVIEW OF LITERATURE

FDA guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make postapproval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and 314.70 (21 CFR 314.70). The guidance covers recommended reporting categories for postapproval changes for drugs other than specified biotechnology and specified synthetic biological products.[1] Lokesh et al (2015) worked on identifying the existing policies and procedure in this area and understanding the underlying concepts for post approval compliance for licenses pertaining to marketing authorization. The study compared and contrasted policies and procedures of regulatory authorities in India, US, EU, Saudi Arabia and Singapore. The major finding of the study indicates that though change management plays a crucial role in the lifecycle of a pharmaceutical. However, lack of defined framework coupled with lack of comprehension of the same has increased the cost of compliance resulting stepmotherly treatment being mitigated towards compliance and license maintenance. The initiatives by the ICH with drafting of ICH Q12 guidelines is a welcome step forward and may help the pharmaceutical industry to comply with the regulations.[2]

Meter et al (2001) discussed about generic products become more available for the treatment of psychiatric disorders, clinicians must stay abreast of the U.S. Food and Drug Administration (FDA) requirements for the approval of generic drug products. The FDA declares that pharmaceutical equivalents only are therapeutically equivalent, and pharmacokinetic data are all that is usually required to determine therapeutic equivalence.

The rationale behind the overall concept of bioequivalence is that if 2 pharmaceutical equivalents provide identical plasma concentration-time profiles in humans, there is no evidence to demonstrate that the 2 identical dosage forms will exhibit a difference in safety and efficacy. This article reviews current terminology used in abbreviated new drug applications for generic products, typical bioequivalence study designs, and FDA bioequivalence guidance for clozapine.[3]

Weisblatt et al (2014) discussed that courts have afforded patent holders broad discretion to choose where to sue Abbreviated New Drug Application (ANDA) filers. Patent holders' assertions of jurisdiction have typically rested on general personal jurisdiction theories, frequently based on an ANDA filers' conduct within the state, including sales, submission to previous lawsuits, and assignments of agents to accept service of process. Consequently, manyANDA cases have taken place in the Districts of Delaware or New Jersey, or where the patent holder is incorporated, despite the ANDA filer's incorporation in a different state. However, since the Supreme Court's decision in Daimler AG v. Bauman, options for the exercise of personal jurisdiction over ANDA filers have narrowed. This article examines what Daimler means for future ANDA filers, and highlights how many patent holders have failed to take this change into account.[4]

A marzo et al (1997) discussed that Pharmacokinetics is a relatively young branch of the life sciences, which has developed rapidly in the last 15-20 years, thanks to a series of analytical achievements that have allowed drug concentrations to be measured in biological matrices with highly selective and sensitive methods. Most old drugs and all new drugs have been investigated in depth to determine their absorption, distribution, metabolism and elimination. This has produced a huge body of data which have characterized drugs through so-called fingerprint parameters. Today, pharmacokinetics plays a vital role throughout drug development from initial non-clinical studies to clinical trials. In new drug development, simultaneous efforts in pharmacodynamic and pharmacokinetic studies have produced a high degree of synergy, the most useful expression of which is the identification of a therapeutic window, where this can be achieved. Dose linearity/proportionality, gender effect, metabolism and possible polymorphism, studies on neonates/children and on elderly and diseased patients and the population approach, relative and absolute bioavailability, possible interactions and the possible presence of a deep compartment in the distribution are other important applications of pharmacokinetics. Major new developments in pharmaceutical technology which have produced controlled- release delivery systems and the market introduction of generics would never have occurred but for the active contribution of pharmacokinetics. This review is devoted to the investigations needed to prepare appropriate pharmacokinetic registration files for new drug applications (NDAs) and abbreviated or abridged new drug applications (ANDAs) required for generic drugs. Scientific literature,

operating guidelines and personal experience are the basis of this review, which describes a number of relevant examples in several specific areas.[5]

Nagori et al (2011) discussed that Generic drugs are identical or bioequivalent versions of the brand name drugs. They are the economic alternative of the costlier brand name drugs. This article presents a general overview of the procedure and regulatory aspects relating to generic drug approval in the US. A computerized search was conducted to find literature on generic drug approval in the US. The literature was searched using the following key words: generic drug, brand name drug, Hatch-Waxman Act, Medicare Act, NDA, ANDA, CTD and exclusivity. The search results were filtered for the literature describing and analyzing the procedure and regulatory provisions for generic drug approval in the US. After the screening total 19 applicable literature remained. In the US standardized procedures for the recognition of generic drugs have been laid down under the Drug Price Competition and Patent Term Restoration Act, 1984 (the Hatch-Waxman Act). Provisions of this Act such as patent challenge, patent term extension and data exclusivity have created profound effects on the approval, sale and distribution of the pharmaceuticals in the US. The Hatch-Waxman Act is an excellent piece of legislation that takes care of the rights of both the brand name and generic drug companies. This article presents only an overview of generic drug approvals and for all practical purposes official resources should be referred.[6]

FDA's (2019) Center for Drug Evaluation and Research's (CDER) annual report, Advancing Health Through Innovation: New Drug Therapy Approvals, reporting our Center's notable new drug approvals to the American public, and illustrating CDER's role in bringing innovative new drug therapies that are safe and effective to patients in need. [7]

FDA guidelines (2022) Under section 506A of the Federal Food, Drug, and Cosmetic Act (FD&C Act), certain changes in the conditions described in approved ANDAs require an approved supplemental application before the change may be made. See also
21 CFR 314.70 and 314.97; Guidance for Industry, *Changes to an Approved NDA or ANDA*.[8]

FDA guidelines (2022) states that the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Hatch-Waxman Amendments, established the approval pathway for generic drug products, under which applicants can submit an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Hatch-Waxman Amendments include provisions that involve patents and exclusivities related to new drug applications, and 180-day exclusivity for certain ANDA applicants. As a general matter, the Food and Drug Administration (FDA or the Agency) has implemented these statutory provisions within the context of application-specific decisions. In certain circumstances, FDA has received requests from applicants and other stakeholders for FDA's communications related to such decisions. FDA intends to publish "frequently requested" communications (5 U.S.C. §552(a)(2)(D)). FDA may also, proactively, publish communications that it determines may be of general interest after addressing any concerns related to the disclosure of proprietary information.[9]

FDA guidelines (2018) states that The Code of Federal Regulations (CFR) is a codification of the general and permanent rules published in the Federal Register by the Executive departments and agencies of the Federal Government.. Title 21 of the CFR is reserved for rules of the Food and Drug Administration. Each title (or volume) of the CFR is revised once each calendar year. A revised Title 21 is issued on approximately April 1st of each year and is usually available here several months later.[10]

AIM AND OBJECTIVE

This aim and objective of the present work is to discuss about the changes to approved nda and anda. This work provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make postapproval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and § 314.70 (21 CFR 314.70). The guidance covers recommended reporting categories for postapproval changes for drugs other than specified biotechnology and specified synthetic biological products. It supersedes the guidance of the same title published November 1999. Recommendations are provided for postapproval changes in

(1) Components and composition,

(2) Manufacturing sites,

(3) Manufacturing process,

(4) Specifications,

(5) Container closure system,

(6) Labeling,

(7) Miscellaneous changes and

(8) Multiple related changes.

DISCUSSION

1. Original ANDAs

A. Primary Assessors

- Primary assessments are to evaluate and recommend whether an ANDA meets the regulatory requirements for approval.

- Primary assessors use the technical (sub)discipline's critical attributes templates and assessment tools, when available, to assess whether the ANDA meets the regulatory approval requirements. These templates and assessment tools may constitute the primary assessment documentation or may be incorporated within an assessment document.

- When the primary assessor needs to incorporate information from the ANDA into the assessment document template, the best approach is to document by reference, either by hyperlink5 or by section and page number. For example, primary assessors do not need to provide a lengthy, detailed summary of a drug product method validation report in their assessment. Instead, primary assessors can evaluate the report, reference the appropriate section of the ANDA that contains the report. (e.g., section 3.2.P.5.3), cite the page number of the appropriate section, and document their evaluation of the submitted data.

If the primary assessor determines it is not the best approach to document by reference, the primary assessor should briefly and concisely summarize key information in the ANDA (e.g., tables and bullet points may be used to convey summarized information) and reference the section of the ANDA where this information can be found.

- Primary assessors keep copying and pasting to a minimum. Primaryassessors should not copy and paste ANDA content into the assessment template or document unless it is essential or more efficient to do so (e.g.,in a specification table).

- Primary assessors do not rewrite, reorganize, reassemble, or remediate the ANDA. As described in FDA's draft guidance for industry Good ANDA Submission Practices, it is the ANDA applicant's responsibility to submit a high-quality and complete ANDA.

- Primary assessors focus on relevant information (i.e., information that is necessary to ensure that the ANDA meets the regulatory requirements for approval) in their specific discipline. Information that is scientifically or academically interesting but is not needed to make a regulatory decision is not relevant. In other words, primary assessors should focus on issues in their specific discipline that are need to know and not nice to know.

- The extent of the assessment and related documentation should be proportionate to 1) the novelty, complexity, and level of potential risk to quality posed by product attributes or process

characteristics and (2) whether the decision will establish a precedent or new policy. If primary assessors have questions about the appropriate extent of their assessment and documentation, they consult their supervisor. If the ANDA meets the regulatory requirements for approval, the primary assessor recommends approval.

- If the ANDA does not meet the regulatory requirements for approval, the primary assessor's communication to the applicant references the application and explains what deficiencies must be corrected for the ANDA to be approvable.

The primary assessor:

- Ensures that the discipline review letter or complete response letter refers to a specific location within the ANDA to provide a point of reference for the deficiency
- Identifies any omitted information or explains the problem with the information submitted
- Explains the actions necessary for the applicant to resolve the deficiency (including alternative approaches, if applicable)
- Explains why the requested information or revision is needed (i.e., the communication should clearly reference the ANDA and explain what deficiencies must be corrected for the ANDA to be approvable and why a major or minor amendment is necessary to respond to each deficiency (e.g., by referencing guidance documents))
- If the communication is a discipline review letter, the primary assessor follows discipline procedures regarding next steps. If the communication is a complete response letter, the primary assessor forwards the ANDA to the secondary assessor.

B. Secondary Assessors

- Secondary assessments provide scientific and regulatory oversight of primary assessments, specifically to ensure the quality of the technical assessment, the quality of the communication to the applicant, and consistency with similar assessments and current policies and procedures.
- The secondary assessor should assess the assessment, not conduct the assessment.
- The extent of the secondary assessment reflects the experience and expertise of the primar assessor; the novelty, complexity, and level of potential risk to quality posed by product attributes or process characteristics; and whether the decision would establish a precedent.
- After the secondary assessor concurs with the primary assessment, he or she forwards the ANDA for the next steps leading to a regulatory action.

C. Division Directors

- The division director ensures that the division is adhering to good ANDA assessment practices as outlined in this MAPP.

- The division director ensures consistency across teams and within his or her specific (sub)discipline.

- Absent unique circumstances, the division director does not redo primary or secondary assessments or dive down into the ANDA or assessment.

- The division director proactively raises emerging issues and serves as a resource to assessors for consultation on novel, complex, or high-risk products and policy- and precedent-setting decisions.6 If the division director identifies an emerging policy issue, he or she should notify the Office of Generic Drug Policy or the Office of Policy for Pharmaceutical Quality, as appropriate.

REQUIREMENTS	US	EU	INDIA
Agency	USFDA	1.EMEA 2.CHMP 3.National Health Agencies	DCGI
Registration Process	One Registration Process	Multiple Registration Process: 1.Centralised Procedure 2.De-Centralised Procedure 3.Mutual Recognition Procedure and 4.National Procedure	One Registration Process
TSE/BSE Study	Study data not required	Study data required	Study data required
Braille code	Not required on labelling	Required on labelling	Not required on labelling
Post approval Changes	1.Minor 2.Moderate 3.Major	1.Type-IA Variation 2. Type-IAIN Variation 3. Type-IB Variation 4. Type-II Variation	1.Moderate 2.Major

I. BACKGROUND

This guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make post approval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and 314.70 (21 CFR 314.70). The guidance covers recommended reporting categories for post approval changes for drugs other than specified biotechnology and specified synthetic biological products. It supersedes the guidance of the same title published November 1999. Recommendations are provided for postapproval changes in

(1) Components and composition,

(2) Manufacturing sites,

(3) Manufacturing process,

(4) Specifications,

(5) Container closure system, and

(6) Labeling, as well as (7) Miscellaneous changes and

(8) Multiple related changes.

This guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) who intend to make post approval changes in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and 314.70 (21 CFR 314.70). The guidance covers recommended reporting categories for post approval changes for drugs other than specified biotechnology and specified synthetic biological products. It supersedes the guidance of the same title published November 1999. Recommendations are provided for postapproval changes in (1) components and composition, (2) manufacturing sites, (3) manufacturing process, (4) specifications, (5) container closure system, and (6) labeling, as well as (7) miscellaneous changes and (8) multiple related changes.

This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

Entitled Changes to an Approved Application for Specified Biotechnology and
Specified Synthetic Biological Products (July 1997). On November 21, 1997, the
President signed the Food and Drug Administration. Modernization Act of 1997 (the Modernization Act).3 Section 116 of the

Modernization Act amended the the Act by adding section 506A, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. The FDA has revised its regulations on supplements and other changes to an approved application (21 CFR 314.70) to conform to section 506A of the Act.

This guidance does not provide recommendations on the specific information that should be developed by an applicant to assess 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, bioequivalence) of a drug product as these factors may relate to the safety or effectiveness of the drug product. An applicant should consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a givenchange.

CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances, that provide recommendations on reporting categories. To the extent that the recommendations on reporting categories in this guidance are found to be inconsistent with guidances published before this guidance was finalized, the recommended reporting categories in such previously published guidances are superseded by this guidance. This guidance does not provide extensive recommendations on reporting categories for components and composition changes (see section V). Therefore, recommended reporting categories for components and composition changes provided in previously published guidances, such as the SUPAC guidances, still apply. Section 506A of the Act and § 314.70(c) provide for two types of changes-being• effected supplements (see section II), while previously there was only one type. It is important for applicants to use this guidance to determine which type of changes-being-effected supplement is recommended. CDER intends to update the previously published guidances to make them consistent with this guidance.

If guidance for either recommended reporting categories or information that should be submitted to support a particular change is not available, the appropriate CDER chemistry or microbiology review staff can be consulted for advice.

FDA's guidance documents, in general, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. REPORTING CATEGORIES

Section 506A of the Act and § 314.70 provide for four reporting categories that are distinguished in the following paragraphs. 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 effectiveness of the drug product. 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, a Prior Approval Supplement (§314.70(b)). An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled, a Prior Approval Supplement - Expedited Review Requested (314.70(b)(4)). FDA is most likely to grant requests for expedited review based on extraordinary hardship for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

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. There are two types of moderate change. One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product

made using the change. This type of supplement is called, and should be clearly labeled, a Supplement - Changes Being Effected in 30 Days (§ 314.70(c)(3)). The drug product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (314.70(c)(5)(i)). For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (§ 314.70(a)(2) and (c)(4)). If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended to provide the missing information (314.70(c)(5)(ii)).

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 effectiveness of the drug product. The applicant must describe minor changes in its next Annual Report (314.70(d)).

Under 314.70(e), an applicant can submit one or more protocols (i.e., comparability protocols) describing tests, studies, and acceptance criteria to be achieved to demonstrate the absence of an adverse effect from specified types of changes.

A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol that was not approved as part of the original application must be submitted as a prior approval supplement (314.70(e)).

On February 25, 2003, FDA issued a draft guidance on comparability protocols entitled Comparability protocols - Chemistry, Manufacturing, and Controls Information.

III. GENERAL REQUIREMENTS

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application (314.70(a)(1)).

A supplement or annual report must include a list of all changes contained in the supplement or annual report. On the list, FDA recommends that the applicant describe each change in enough detail to allow FDA to quickly determine whether the appropriate reporting category has been used. For supplements, this list must be provided in the cover letter (§ 314.70(a)(6)). In annual reports, the list should be included in the summary section (§ 314.81(b)(2)(i)). The applicant must describe each change fully in the supplement or annual report (314.70(a)(1)).

An applicant making a change to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (CGMP) requirements of the Act (21 U.S.C. 351(a)(2)(B)) and applicable regulations in Title 21 of the Code of Federal Regulations (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant

CGMP validation and recordkeeping requirements and ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

A changes-being-effected supplement providing for labeling changes under 314.70(c)(6)(iii) must include 12 copies of the final printed labeling (§ 314.70(c)(1)). In accordance with 314.70(a)(4), an applicant also must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with §314.70(b) or (c).

Except for supplements providing only for a change in labeling, an applicant must include in each supplement and amendment to a supplement a statement certifying that a field copy has been provided in accordance with 21 CFR 314.440(a)(4) (314.70(a)(5)).

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. Assessment of the Effects of the Change

The holder of an approved application under section 505 of the Act must assess the effects of the change before distributing a drug product made with a manufacturing change (§ 314.70(a)(2)).

For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (section 506A(b), (c)(1), (d)(2)(A), and (d)(3)(A) of the Act).

The type of information that must be included in a supplemental application or an annual report is specified in § 314.70(b)(3), (c)(4), and (d)(3).

1. Conformance to Specifications

An assessment of the effects of a change on the identity, strength, quality, purity, and potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected

by the change conform to the approved specifications.8 A specification is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described (§ 314.3(b)). Conformance to a specification means that the Mailing information for field copies is provided in 21 CFR 314.440(a)(4). FDA recommends that the applicant's home FDA district office referred to in the regulations be the district office where the applicant's headquarters is located. material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. Additional Testing

In addition to confirming that the material affected by manufacturing changes continues to meet its specification, we recommend that the applicant perform additional testing, when appropriate, to assess whether 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 have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the material directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the drug product.

For example:

- Evaluation of changes in the impurity or degradant profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.9
- Evaluation of the hardness or friability of a tablet after certain changes.
- Assessment of the effect of a change on bioequivalence when required under 21
- CFR part 320 could include, for example, multipoint and/or multimedia dissolution profiling and/or an in vivo bioequivalence study.
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

B. Equivalence

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the Identity, Strength, Quality, Purity, and potency of the Recommendations on identifying, qualifying, and reporting impurities can be found in relevant guidances (e.g., ICH Q3B) Impurities in New Drug Products

(November 1996)) drug product. Typically this is accomplished by comparing test results from pre- and postchange material and determining if the test results are equivalent. Simply stated: Is the drug product made after the change equivalent to the drug product made before the change? An exception to this general approach is that when bioequivalence is redocumented for certain ANDA postapproval changes, FDA recommends that the comparator be the reference listed drug. Equivalence comparisons frequently have a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this, as well as for other reasons, equivalent does not necessarily mean identical. Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

C. Adverse Effect

Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment indicates that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, FDA recommends that the change be submitted in a prior approval supplement regardless of the recommended reporting category for the change. For example, a process change recommended for a changesbeing- effected-in-30• days supplement could cause the formation of a new degradant that requires qualification and/or identification.10 The applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. Even so, we recommend that the applicant submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the drug product. During the review of the prior approval supplement, the FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product.

Applicants are encouraged to consult with the appropriate CDER chemistry or microbiology review staff if there are any questions on whether a change in a characteristic would be viewed by CDER as adversely affecting the identity, strength, quality, purity, or potency of the drug product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes requiring a prior approval supplement, unless exempted by regulation or guidance (§ 314.70(b)(2)(i)). The deletion or reduction of an ingredient intended to affect only the color of the drug product may be reported in an annual report (§ 314.70(d)(2)(ii)) of the complexity of the recommendations, but may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

VI. MANUFACTURING SITES

A. General Considerations

CDER must be notified when a manufacturer changes to a manufacturing site that is different from those specified in the approved application (314.70(a)). Sites can include those used by an applicant to

(1) Manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates,

(2) Package drug products,

(3) Label drug products, and

(4) Test components, drug product containers, closures, packaging materials, in- process materials, or drug products. Sites include those owned by the applicant or contract sites used by an

applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered those that perform labeling of the drug product's primary or secondary packaging components.

Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product.

FDA recommends that the supplement or annual report identify whether the proposed manufacturing site is an alternative to or replacement for the site or sites provided for in the approved application.

FDA recommends that a move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, be submitted as a prior approval supplement if the site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2). products, in-process materials, drug substances, or drug substance intermediates or (2) perform primary packaging operations,

Manufacturing or processing drug product would also include the preparation (e.g., sterilization, depyrogenation, irradiation, washing) by the applicant or applicant's contractor of container closure systems or packaging components. Changes in the site used to fabricate packaging components (e.g., bottles) or manufacture packaging materials (e.g., resins) need not be reported to CDER if there are no other changes (e.g., dimensions, compositions, processing aids). If other changes occur, the reporting category should be based on the recommended reporting categories for these changes (i.e., the manufacturing site change does not need to be considered when determining the appropriate reporting category) the potential for adverse effect depends on factors such as the type of drug substance or drug product and operation being performed. Therefore, recommended reporting categories may differ depending on the type of drug product and operations.

Except for the situations described in sections VI.B.4, VI.C.1.b, and VI.D.5, construction activities at a manufacturing site or moving production operations within a building or between buildings at the same manufacturing site do not have to be reported to CDER.

We recommend that a move to a manufacturing site that involves other changes (e.g., process, equipment) be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have 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 effectiveness of the drug product.

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the

type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.

2. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory CGMP inspection for the type of operation being moved.

3. A move to a different manufacturing site for

(1) The manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or

(2) The manufacture or processing of in-process materials with modifiedrelease characteristics. Examples of these types of drug products include modified- release solid oral dosage forms, transdermal systems, liposomal drug products, depot drug products, oral and nasal metereddose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.

4. Transfer of the manufacture of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved drug products. An example:

Certain operations relating to the manufacture, processing, or primary packaging of modified-release solid oral dosage form drug products need not be reported in a prior approval supplement (see sections VI.C.1.c and VI.D.6).

This would be transferring the manufacture of a lyophilized drug product to an existing aseptic process area where no approved lyophilized drug products are manufactured or where the approved lyophilized drug products being manufactured have different container types and/or sizes than the container of the drug product being transferred. See section VI.C.1.b for recommendations for other manufacturing site changes relating to aseptically processed sterile drug substance or aseptically processed sterile drug product.

5. Transfer of the manufacture of a finished drug product sterilized by terminal processes to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility for similar drug product types and processes may be submitted as a changes-beingeffected-in-30-days supplement (see section VI.C.1.a).

C. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes considered to have a moderate 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 effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2), then FDA recommends that the changes listed below

(excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement.

1. Supplement - Changes Being Effected in 30 Days

a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.

b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at

the same or different manufacturing site except as provided for in section VI.B.4.

c. A move to a different manufacturing site for the primary packaging of

(1) any drug product that is not otherwise listed as a major change and

(2) modified-release solid oral dosage form drug products.

d. A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing.

2. Supplement - Changes Being Effected A move to a different manufacturing site for the manufacture or processing of the final intermediate.

D. Minor Changes (Annual Report)

The following are examples of changes considered to have a minimal 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 effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved, then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement (see sections VI.B.1 and 2).

1. A move to a different manufacturing site for secondary packaging.

2. A move to a different manufacturing site for labeling.

3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates other than the final intermediate.

4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application

5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.

6. A move to a different manufacturing site for the ink imprinting of solid oral dosage form drug products.

VII. MANUFACTURING PROCESS

A. General Considerations

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases, there may be a substantial potential for adverse effect regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change must be submitted in a prior approval supplement (section 506A(c) of the Act).

B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have 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 effectiveness of the drug product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.

2. Changes that may affect drug product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

- Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa.
- Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation.
- Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacement steam process with a process using superheated water spray).
- Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.
- Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling. Once this change has been approved, subsequent process changes for similar product types in

the same barrier system or isolator may be submitted as a changes-being-effected-in-30-days supplement.

- Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time.
- Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa.
- Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent beyond the validated limits in the approved application.
- Changes in sterilizer load configurations that are outside the range of previously validated loads.
- Changes in materials or pore size rating of filters used in aseptic processing.

3. The following changes for a natural product:

- Changes in the virus or adventitious agent removal or inactivation methods.
- This applies to any material where such procedures are necessary, including drug substance, drug product, reagents, and excipients.
- For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line.
- For drug substance and drug product, establishment of a new master cell bank or seed.
- Any fundamental change in the manufacturing process or technology from t currently used by the applicant. For example:
- Dry to wet granulation or vice versa.
- Filtration to centrifugation or vice versa.

5. The following changes for drug substance drug substance manufacture.

- Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties.
- imprint code for a solid oral dosage form drug product when the ink as changed is not currently used on CDER-approved drug products.17
- For the purposes of this guidance, natural product refers to materials (e.g., drug substance, excipients) that are derived from plants, animals, or microorganisms, and that are subject to approval under section 505 of the Act. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals).

6. See Attachment C for a discussion of CDER-approved drug products.

7. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.

C. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes considered to have a moderate 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 effectiveness of the drug product.

1. Supplement - Changes Being Effected in 30 Days

a. For drug products, any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance.

b. For drug substances, any change in process and/or process parameters except as otherwise provided for in this guidance.

c. For natural protein drug substances and natural protein drug products:

- Any change in the process, process parameters, and/or equipment except as otherwise provided for in this guidance (e.g., section VII.B.5, VII.D.7).
- An increase or decrease in production scale during finishing steps that involves different equipment.
- Replacement of equipment with equipment of different design that does not affect the process methodology or process operating parameters.

d. For sterile drug products, drug substances, and components, as appropriate:

- Changes in dry heat depyrogenation processes for glass container systems for drug substances and drug products that are produced by terminal sterilization processes or aseptic processing.
- Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating) when additional validation studies for the new parameters should be performed.
- Filtration process changes that provide for a change from single to dual sterilizing filters in series, or for repeated filtration of a bulk.
- Changes from one qualified sterilization chamber to another for in- process or terminal sterilization that result in changes to validated operating parameters (time, temperature, F0, and others).
- Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.

2. Supplement - Changes Being Effected

a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.

b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized drug product.

D. Minor Changes (Annual Report)

The following are examples of changes considered to have a minimal 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 effectiveness of the drug product.

1. For drug products, changes to equipment of the same design and operating principle and/or changes in scale except as otherwise provided for in this guidance (e.g., section VII.C.1.c, VII.D.7).

2. A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.

3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved drug products.

4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified- release dosage form.

5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions).

6. Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged.

7. For natural protein drug products and natural protein drug substances:

- An increase or decrease in production scale during finishing steps that does not involve an equipment change.

- Replacement of equipment with equipment of the same design, operating principle, and capacity with no change in production scale.

8.

VIII. SPECIFICATIONS

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a prior approval supplement unless otherwise exempted by regulation or guidance (314.70(b)(2)(i)). Specifications (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of defining specifications, acceptance criteria are numerical limits, ranges, or other criteria for the tests described. Examples of a test, an analytical procedure, and an acceptance criterion are, respectively, an assay, a specific, fully described high pressure liquid chromatography (HPLC) procedure, and a range of 98.0–102.0 percent. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions.18

A regulatory analytical procedure is the procedure in the approved application that is designated for use in evaluating a defined characteristic of the drug substance or drug product. Section 501(b) of the Act recognizes the analytical procedures in the U.S. Pharmacopeia/National Formulary (USP/NF) as the regulatory analytical procedures for compendial items. Tests and associated acceptance criteria and regulatory analytical procedures in addition to those specified in the USP/NF may be required for approving compendial items (section 505 of the Act).

The applicant may include in its application alternatives to the approved regulatory analytical procedures for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, regulatory analytical procedures are used.

See FDA guidance for industry on the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (November 1994).

In sections B through D below, the use of the term analytical procedure without a qualifier such as regulatory or alternative refers to an analytical procedure used to test materials other than the drug substance or drug product.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes in specifications considered to have 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 effectiveness of the drug product.

1. Relaxing an acceptance criterion except as otherwise provided for in this guidance (e.g., section VIII.C.1.b, VIII.C.1.e).

2. Deleting any part of a specification except as otherwise provided for in this guidance (e.g., section VIII.D.2).

3. Establishing a new regulatory analytical procedure including designation of an alternative analytical procedure as a regulatory procedure.

4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application.

5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to

(1) An HPLC procedure that does not,

(2) Another type of analytical procedure (e.g., titrimetric) that does not, or (3) an HPLC procedure that distinguishes impurities but the limit of detection and/or limit of quantitation is higher.

6. Relating to testing of raw materials for viruses or adventitious agents: (1) relaxing an acceptance criterion,

(2) Deleting a test, or

(3) A change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

C. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes in specifications considered to have a moderate 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 effectiveness of the drug product.

1. Supplement - Changes Being Effected in 30 Days

a. Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes.

b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials prior to the final intermediate, starting materials introduced prior

to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) except as provided for in section VIII.B.6.

c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials prior to the intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency

of the material being tested as the analytical procedure described in the approved application except as provided for in section VIII.B.6.

d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions. For example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling.

e. Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements (§ 314.70(c)(2)(iii)).

2. Supplement - Changes Being Effected

a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess. For example, adding a new test and associated analytical procedure and acceptance criterion.

b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

D. Minor Changes (Annual Report)

The following are examples of changes in specifications considered to have a minimal 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 effectiveness of the drug product.

1. Any change in a specification made to comply with an official compendium, except the changes described in section VIII.C.1.e, that is consistent with FDA statutory and regulatory requirements (§ 314.70(d)(2)(i)).

2. For drug substance and drug product, the addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application or deletion of an alternative analytical procedure.

3. Tightening of acceptance criteria.

4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced prior to the final drug substance intermediate, in-process materials prior to the finalintermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

IX. CONTAINER CLOSURE SYSTEM

A. General Considerations

The potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and the likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct drug product testing for conformance with the approved specification.

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have 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 effectiveness of the drug product.

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved drug product of the same dosage form and same route of administration. For example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER- approved for an ophthalmic ointment.

2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change from an ink and/or

adhesive used on the permeable or semipermeable packaging component to an ink or adhesive that has never been used in a CDER-approved drug product of the same dosage form and same route of administration and with the same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride).

3. A change in the primary packaging components for any drug product when the primary packaging components control20 the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).

4. For sterile drug products, any change that may affect drug product sterility assurance, such as:

- A change from a glass ampule to a glass vial with an elastomeric closure.
- A container closure system that is considered to control the dose delivered to the patient is a container closure system where the system itself, rather than a person, regulates the amount of drug product ultimately delivered to a patient. A container closure system where a person controls the amount of drug product administered or that allows verification that the appropriate amount has been administered (e.g., number of tablets, milliliters of liquid) is not considered a container closure system that controls the dose delivered to the patient.
- Some of these identified changes, depending on the circumstances, may have to be submitted as original NDAs or ANDAs instead of as supplements. Applicants can consult the appropriate CDER chemistry division/office if there are questions.
- A change to a flexible container system (bag) from another container system.
- A change to a prefilled syringe dosage form from another container system.
- A change from a single unit dose container to a multiple dose container system.
- Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels).
- Changes in the size and/or shape of a container for a sterile drug product

5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases) or a change in the composition of, or the addition of, a secondary packaging component that may affect the impurity profile of the drug product.

6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.

C. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes considered to have a moderate 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 effectiveness of the drug product.

1. Supplement - Changes Being Effected in 30 Days

a. A change to or in a container closure system, except as otherwise provided for in this guidance, that does not affect the quality of the drug product.

b. Changes in the size or shape of a container for a sterile drug substance.

c. A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a nonsterile drug product in a unit-of-use container.22

2. Supplement - Changes Being Effected

A unit-of-use container is one that contains a specific quantity of a drug product and is intended to be dispensed to the patient without further modification except for the addition of appropriate labeling.

a. A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2), without a change from one container closure system to another (314.70(c)(6)(ii)).

b. A change in the labeled amount (e.g., grams, milliliters) of drug product for a nonsterile drug product in a multiple-unit container,23 except for solid dosage forms (see section IX.D.3).

c. A change in or addition or deletion of a desiccant.

D. Minor Changes (Annual Report)

The following are examples of changes considered to have a minimal 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 effectiveness of the drug product.

1. A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium (314.70(d)(2)(v)).

2. A change in the size and/or shape of a container for a nonsterile solid dosage form (§ 314.70(d)(2)(iv)).

3. A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams) of nonsterile solid dosage form in a multiple-unit container.

4. The following changes in the container closure system of solid oral dosage form drug products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER- approved solid oral dosage form drug products:24

 Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.

A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion. This type of container is not distributed directly to patients but is used by health care practitioners who dispense the drug product in smaller amounts to a patient in accordance with a physician's instructions.

For sections IX.D.4 to IX.D.7, changes in the container closure system that result in drug product contact with a component material that has never been used in any CDER- approved drug product of the same type should be submitted as a changes-being• effected-in-30-days supplement (section IX.C.1) or prior approval supplement (section IX.B.1).

Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) container to another HDPE container).

- Changes in packaging materials used to control odor (e.g., charcoal packets).
- Changes in bottle filler (e.g., change in weight of cotton or amount used)without changes in the type of filler (e.g., cotton to rayon).
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal (e.g., heat induction seal).
- A change in an antioxidant, colorant, stabilizer, or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage form drug products.
- A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the drug product.

5. The following changes in the container closure system of nonsterile liquid drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid drug products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER- approved liquid topical drug products):

- Adding or changing a child-resistant closure, changing from cap.
- A change in or addition of a cap liner. packs) for nonsterile solid dosage form drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved drug products of the same type (e.g., solid oral dosage form, rectal suppository).

7. The following changes in the container closure system of nonsterile semisolid drug products as long as the new package provides the same or better protective properties and any new primary

packaging component materials have been used in and been in contact with CDER-approved semisolid drug products:

- Changes in the closure or cap.
- Increasing the wall thickness of the container.
- A change in or addition of a cap liner.
- A change in or addition of a seal.
- A change in the crimp sealant.

8. A change in the flip seal cap color as long as the cap color is consistent with any established color coding system for that class of drug products.

X. LABELING

A. General Considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. In accordance with § 314.70(a)(4), an applicant must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) or (c) of § 314.70. All labeling changes for ANDA drug products must be consistent with section 505(j) of the Act.

B. Major Changes (Prior Approval Supplement)

Any proposed change in the labeling, except changes designated as moderate or minor by regulation or guidance, must be submitted as a prior approval supplement (§ 314.70(b)(2)(v)(A)). If applicable, any change to a Medication Guide required under 21 CFR part 208, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv), must be submitted in a prior approval supplement (§ 314.70(b)(v)(B)). The following list contains some examples of changes currently considered by CDER to fall into this reporting category.

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.

2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.

3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.

4. Changes based on data from preclinical studies.

5. Revision (expansion or contraction) of population based on data.

6. Claims of superiority to another drug product.

7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

C. Moderate Changes (Supplement - Changes Being Effected)

Under § 314.70(c)(6)(iii), a changes-being-effected supplement must be submitted for any labeling change that (1) adds or strengthens a contraindication, warning, precaution, or adverse reaction, (2) adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage, (3) adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the drug product, (4) deletes false, misleading, or unsupported indications for use or claims for effectiveness, or (5) normally requires a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision. A changes being-effected supplement that provides for a labeling change under §§ 314.70(c)(6)(iii) must include 12 copies of final printed labeling (§ 314.70(c)(1)). The following list includes some examples of changes currently considered by CDER to fall into this reporting category.

1. Addition of an adverse event due to information reported to the applicant or Agency.

2. Addition of a precaution arising out of a postmarketing study.

3. Clarification of the administration statement to ensure proper administration of the drug product.

D. Minor Changes (Annual Report)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report (§ 314.70(d)(2)(ix) and (d)((2)(x)) . The following list includes some examples currently considered by CDER to fall into this reporting category.

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201) without a change in the content of the labeling.

2. Editorial changes, such as adding a distributor's name.

3. Foreign language versions of the labeling if no change is made to the content of the approved labeling and a certified translation is included.

4. Labeling changes made to comply with an official compendium.

XI. MISCELLANEOUS CHANGES

A. Major Changes (Prior Approval Supplement)

The following are examples of changes considered to have 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 effectiveness of the drug product.

1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug(§ 314.70(b)(2)(ii)).

2. Addition of a stability protocol or comparability protocol.

3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2).

4. An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol.

5. Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application (§ 314.70(b)(2)(viii)).

B. Moderate Changes (Supplement - Changes Being Effected)

The following are examples of changes considered to have a moderate 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 effectiveness of the drug product.

1. Supplement - Changes Being Effected in 30 Days

Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be submitted in a changesbeing-effected-in-30-days supplement even if the extension is based on data obtained under a protocol approved in the application.

2. Supplement - Changes Being Effected

No changes have been identified.

C. Minor Changes (Annual Report)

The following are examples of changes considered to have a minimal 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 effectiveness of the drug product.

1. An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application (314.70(d)(2)(vi)).

2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period.

3. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances.

4. Non-USP reference standards:

- Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application.
- Tightening of acceptance criteria for existing reference standards to provide greater assurance of drug product purity and potency.

XII. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes or a components and composition change may necessitate a change in a specification. For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the submission be in accordance with the most restrictive of the categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the submission be in accordance with the reporting category for the individual changes.

ATTACHMENT A: MANUFACTURING SITES

All owners or operators of all drug establishments (not exempt by regulation) that engage in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs are required to register with the FDA (21 CFR 207.20). An establishment means a place of business under one management at one general physical location (§ 207.3(a)(7)). A general physical location is reasonably construed to include separate buildings within the same city if the activities in the buildings are closely related to the same business enterprise, are under the supervision of the same local management, and are all inspected at the same time (ORA Field Management Directive No. 132).

For the purposes of determining the reporting category for moves between buildings, the terms same manufacturing site and different manufacturing site mean: Domestic Establishments

Same manufacturing site:

- The new and old buildings are included under the same drug establishment registration number

- The same FDA district office is responsible for inspecting the operations in both the new and old buildings.

Different manufacturing site:

- The new and old buildings have different drug establishment registration numbers or
- Different FDA district offices are responsible for inspecting operations in the new and old buildings.

For domestic establishments, the terms same manufacturing site and different manufacturing site supersede the terms contiguous campus, same campus, and different campus as used in the SUPAC guidances. Foreign establishments are not currently required to register with the FDA. On May 14, 1999, FDA published a proposed rule to require registration of foreign establishments (64 FR 26330). Until registration of foreign establishments is required, same and different manufacturing sites mean:

Same manufacturing site:

A contiguous or unbroken site or a set of buildings in adjacent city blocks.

Different manufacturing site:

The new and old buildings are not on a contiguous site or not in adjacent city blocks.

ATTACHMENT B: TYPE OF OPERATION AND CGMP INSPECTIONS

Section VI states that a change to a different manufacturing site should be submitted in a prior approval supplement when

(1) The new manufacturing site has never been inspected by FDA for the type of operation being moved,

(2) The move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years, or

(3) The new manufacturing site does not have a satisfactory current good manufacturing practice (CGMP) inspection for the type of operation being moved.

A profile class system is used by FDA to assist in

(1) Managing the CGMP inspection process,

(2) Evaluating the findings and the compliance follow-up needed, and

(3) Communicating the results of inspections. A profile class can relate to the manufacture of a particular dosage form (e.g., large volume parenterals, oral liquids), type of drug substance (e.g.,

sterile bulk by chemical synthesis), or specific function performed at a site (e.g., control testing laboratory). There are profile class codes for major categories of drug substance processes, dosage forms, and manufacturing functions (see table below).

However, the system is not comprehensive for all operations performed in the pharmaceutical industry (see not elsewhere classified (NEC) profile class code).

The term type of operation refers to the specialized or even unique conditions and practices that are employed to manufacture a class or category of drug substance or drug product or to perform a limited segment of the manufacturing process.

These conditions and practices exist and are performed within the framework of CGMPs, along with general conditions and practices that contribute to the manufacture of all drug products at a given manufacturing site. The conditions

and practices, both general and specific, are inspected to evaluate the CGMP acceptability of a manufacturing site. A wide variety of classes or categories of drug substances and drug products may be produced at a manufacturing site, or the manufacturing site may only produce a single class of drug substance and/or drug product or perform a limited segment of a manufacturing process. Each type of operation is represented by a profile class code.

Generally, a satisfactory CGMP status for a profile class code is used to communicate a satisfactory CGMP clearance for all of the products and for all of the operations included within the category that code represents. Thus the profile class code for a particular dosage form or type of drug substance is used to communicate the CGMP status for all aspects of manufacturing, processing, packing, or holding that are performed at the specific manufacturing site relating to that particular dosage form or type of drug substance, including packaging and labeling operations, testing, and quality control.

The profile class code for a particular dosage form or type of drug substance is also used to communicate the CGMP status for manufacturing sites that produce in- process material (e.g., controlled-release beads), package drug products, or label drug products, even if these are stand-alone (e.g., contractor) operations.

A few profile class codes that describe certain types of operations (see items in boldface in table) are provided to report the CGMP status for contractor firms whose only function in the manufacturing process is to perform this operation.

If one of these operations (e.g., steam sterilization process) is performed at the manufacturing site involved in producing the drug product/drug substance, the CGMP status for that operation is reported as part of the profile class code for the particular dosage form or type of drug substance. For example, a manufacturing site producing a terminally sterilized small volume parenteral drug product would be reported with the profile class code for the dosage form (SVT), not by the profile code for the sterilization process (SSP).

Examples of postapproval manufacturing site changes and recommended reporting categories:

- An applicant wants to move the manufacture of an immediate-release tablet (TCM) to a different manufacturing site that currently manufactures, and has satisfactory CGMP status for, capsules (CHG) and powders for oral solution (POW). This manufacturing site change should be submitted in a prior approval supplement because the new manufacturing site does not have a satisfactory CGMP inspection for immediate-release tablets.
- An applicant wants to contract out packaging operations for immediate-release tablets (TCM) and capsules (CHG) and modified-release capsules (CTR). The potential contract packager has a satisfactory CGMP status for immediate- release and modified-release capsules but has never packaged immediate- release tablets. The packaging site change for the immediate- release tablet drug products should be submitted in a prior approval supplement. The packaging site change for the capsule drug products should be submitted as recommended in section VI of this guidance for packaging sites with a satisfactory CGMP inspection.
- An applicant wishes to consolidate product testing to a single analytical laboratory at a manufacturing site. This manufacturing site produces various solid oral dosage form drug products, has an operational analytical laboratory currently at the site, and satisfactory CGMP inspections for the manufacturing occurring at the facility. Some of the drug products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories (and other operations in boldface in the table) are not inspected on a dosage form/type of drug substance specific basis. The satisfactory CGMP inspection of the analytical laboratory, which was performed as part of the CGMP inspection for manufacture of the solid oral dosage form drug products, is considered to apply to all dosage forms, including those not actually produced at the site. The consolidation can be submitted in a changes-being-effected-in- 30-days supplement if the change is consistent with the recommendations in sectionVI.C.1.d

ATTACHMENT C: CDER-APPROVED DRUG PRODUCTS

In several places throughout the guidance, different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved drug products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a drug product approval because similar subsequent changes then have a reduced 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 effectiveness of the drug product. For example, certain changes in the container closure systems of solid oral dosage form drug products may be included in an annual report as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER- approved solid oral dosage form drug products (see section IX.D.4). If the new primary packaging component material has not been used in or has not been in contact with CDER- approved solid oral dosage form drug products, then submission of the change in an annual report is not recommended.

CDER-approved drug products are considered those drug products subject to an approved NDA or ANDA. Some information on which components/materials are used in CDER-approved products is available from the Agency (e.g., FDA, CDER, Inactive Ingredient Guide, 1996, Division of Drug Information Resources). When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER- approved drug product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved drug product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved drug product of the same dosage form and route of administration, the applicant has the option of submitting the change for a single NDA or ANDA using the higher recommended reporting category and, after approval, submitting similar changes for other NDAs and ANDAs using the lower recommended reporting category.

Example: 1

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED IN 30 DAYS (QUALITY FACILITY AND CHEMISTRY INFORMATION PROVIDED)

Office of Generic Drugs, CDER, FDA Kathleen Uhl, MD, Director Document Control
Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2810
(Provide for the Addition of a Contract Analytical Testing Facility) Dear Dr. Uhl:

xxxx wishes to supplement the Abbreviated New Drug Applications (ANDA's) listed in Attachment A of this letter to provide for an additional contract analytical testing facility to be used by the approved drug product manufacturer, xxxx Specifically, xxx wishes to add xxxxxx as a contract testing facility for the testing of the packaging material Desiccants for Lead testing as result of a recent USP monograph update. Please note that xxx is an approved drug product manufacturing facility in a number of xxxxx ANDAs xxx cGMP and Debarment certifications are provided in Section 3.2.P.3.1 and 1.3.3 respectively. Contact details and responsibilities are listed in the following table.xxxx has confirmed that a satisfactory cGMP inspection was completed, and a copy of the cover letter from the FDA establishment inspection report is provided in Section 3.2.P.3.1.

Please note that MLL, Nashik will continue to perform the official release of Desiccants utilized in each respective ANDA.

Other changes will be updated in the next Annual Report for each affected ANDA to incorporate the establishment information and specific testing performed by xxxxas provided in the table above.

Additionally, the packing material specifications that were revised in accordance with the USP will be submitted in the next Annual Report for each affected ANDA. This approach has been was discussed with Dr. Olugbenga Okubadejo, of your Office, in a telephone call on August 24, 2016.

In accordance with Section VI.C.1.d. of the Agency's Guidance for Industry, Changes to an Approved NDA or ANDA (April 2004), this change to add an analytical testing facility is being reported as a Special Supplement - Changes Being Effected in 30 Days as the following criteria are met:

(1) Previously approved test methods or compendial procedures will be used;

(2) There are no outstanding post approval commitments related to the test methods; and

(3) The alternate testing site is capable of performing the intended tests. As such, xxxx intends to implement this change on, or about, 30 days from the date of submission of this supplement.

All files in this supplemental application have been scanned utilizing Symantec antivirus software and are free of known viruses. All correspondence regarding this supplemental application should be directed to the attention of the undersigned **Example 2:**

PRIOR APPROVAL SUPPLEMENT

(QUALITY, FACILITY AND CHEMISTRY INFORMATION PROVIDED) Provide for an Alternate Drug Substance Source.

Example 3:

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED IN 30 DAYS

(CHEMISTRY INFORMATION PROVIDED)

Provide for Changes to the Manufacturing Process for the API XXXXX

This guidance has been prepared under the direction of the Chemistry, Manufacturing and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

Paperwork Reduction Act Public Burden Statement: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0538 (until August 31, 2005).

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h – APPLICATION TO MARKET A NEW OR

ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE

Field 1: DATE OF SUBMISSION

Enter the date the submission is being submitted to the FDA. The date entered should match the date of the cover letter for the submission. Fields 2–6: APPLICANT INFORMATION

This section should include the name, street address, applicant Data Universal Numbering System (DUNS) number, telephone and facsimile numbers of the person or legal entity submitting the application. For biologic products, the name of applicant in Field 2 is the name of the person or legal entity to whom the license will be issued. Enter the U.S. license number, if previously issued, in the appropriate field. Enter the name, street address, applicant DUNS number, US Agent DUNS and telephone number of the person and legal entity authorized to represent a non-U.S. applicant in Field 6.

Fields 7–15: PRODUCT DESCRIPTION

This section should include all the information necessary to identify the product that is the subject of this application or submission.

Field 7: NDA, ANDA, OR BLA APPLICATION NUMBER

Provide the six-digit application number. For application numbers less than six-digits, the application number should be preceded using zeros (i.e., for NDA 12345 enter 012345). Field 8: SUPPLEMENT NUMBER

Provide the four-digit supplement number with preceding zeros for supplement numbers that are less than four-digits (i.e., for Supplement 1 enter 0001).

Field 15A: PROPOSED INDICATION FOR USE

For original and efficacy supplemental applications only (including resubmissions to these application types),

provide the indication(s) proposed within the application. Indicate if the proposed indication is for a rare disease (prevalence <200,000 U.S. patients). Indicate if the product proposed within the application (i.e. not the reference listed drug for an ANDA) has an FDA Orphan Drug Designation and if so; provide the six-digit Orphan Designation number. If the submission is not an original application or efficacy supplement, select

'No' in response to 'Is this indication for a rare disease?' Use the Continuation Page if there are more than one proposed indications for use by adding one indication per entry and providing rare disease/Orphan Drug Designation information for each entry, as applicable. If continuation pages are not needed, click on the 'Remove Continuation Page' button at top/bottom of form.

Field 15B: SNOMED CT INDICATION DISEASE TERM(S)

For each original and efficacy supplemental applications only (including resubmissions to these application types), provide the SNOMED CT coded disease term (e.g., 38341003 | Hypertensive disorder, systemic arterial (disorder) |) for the indication provided in Field 15A. To look up the indication's SNOMED CT coded disease term:

1. Navigate to http://browser.ihtsdotools.org/.
2. Under Local Extensions, select 'Go Browsing United States edition'.
3. Select the 'Search' tab located in the upper left hand of page.
4. Enter the disease term in the search field.
5. Check the box 'Group by concept'.
6. Select the single most appropriate term for the indication.
7. Select the 'Expression' tab located in the upper right hand of page.
8. Copy the entire text that appears under the heading 'Pre-coordinated Expression.
9. Paste the copied SNOMED CT disease term into Field 15B of Form FDA 356h.
10. For additional indications, use the continuation page for #15 and repeat these steps. Fields 16–30: APPLICATION INFORMATION

Fields 16–18: Identify the appropriate application type. Field 19: 351(k) BASIS FOR SUBMISSION

If the application is a 351(k) BLA, provide the name of the biological reference product that is the basis for the application and the holder of the licensed application.

Field 20: ANDA OR 505(b)(2) BASIS FOR SUBMISSION

If the application is a 505(b)(2) NDA, provide the name(s) and application number(s) of the listed drug(s) that you are relying on. If you are submitting an ANDA, please provide the name and application number for the reference listed drug (RLD). If the reference standard (RS) for the ANDA (generally identified in the Orange Book) differs from the RLD, information about the RS should not be provided on the 356h, but should be included elsewhere in the application (e.g., sections 1.12.11)."

Field 21: SUBMISSION TYPE

For original applications, select 'Original'. For all other submission types, select any of the submission types listed that apply, or specify the type of submission under "Other" if otherwise not listed. See also 21 CFR 314.3(b).

Original: An application for which FDA has never issued an approval letter;

Labeling Supplement: A supplemental application for labeling changes to an approved product as described under 21 CFR 314.70 and 21 CFR 601.12 that does not otherwise qualify as another type of supplement (e.g., Efficacy, CMC, REMS);

CMC Supplement: A supplemental application for chemistry, manufacturing, and control (CMC) changes to an approved product as described under 21 CFR 314.70, 21 CFR 314.71, 21

CFR 314.72, and 21 CFR 601.12, including CMC supplements with corresponding labeling changes;

Efficacy Supplement: A supplemental application for changes to an approved product from among the following changes: new or modified indication; new or revised dose or dosing regimen; new route of administration; comparative efficacy claim naming another product; significant alteration in the patient population; switch of marketing status from prescription to over-the-counter use; traditional approval of a product originally approved under Subpart H (Accelerated Approval) or Subpart I (Animal Rule); labeling or manufacturing change requiring clinical data for approval;

Annual Report: See 21 CFR 314.81(b)(2) for NDAs and 21 CFR 601.12(d) for BLAs; Product Correspondence: Any communication or general correspondence related to an application (e.g., routine administrative changes, donor re-entry requests, lot distribution reports, license reissuance requests, meeting requests) that is not an amendment to a pending application. Provide description of the content or intent of the Product Correspondence in Field 27 (Reasons for the Submission);

REMS Assessment Methodologies and Study Protocols: A submission containing information on methodological approaches and study protocols use to assess a REMS program; REMS Assessment Report: A submission containing information and data to support if the goal of each strategy is being met; modifications to the REMS or revisions to the REMS assessment plan are needed, including the timing of the REMS assessments; and whether the REMS is still necessary to ensure the benefits outweigh the risks of the drug;

REMS Supplement: A supplemental application proposing a new Risk Evaluation and Mitigation strategy (REMS) or modifications (major and/or minor) to an approved REMS; Post Marketing Requirements or Commitments: A submission containing information related to Post marketing requirements or commitments.

(e.g., nonclinical protocol, final study report); Periodic Safety Report: Periodic reports (Periodic Adverse Drug Experience Reports (PADERs)) of adverse drug or biological product experience as described under 21 CFR 314.80(c)(2),

21 CFR 314.98, and 21 CFR 600.80(c)(2), including those in Periodic Safety Update Report (PSUR) format; Request for Proprietary Name Review: A submission containing a request for proprietary name review; Human Factors (Specify Type): Select check box and specify what type of HF information is being submitted in “Specify Type” (e.g. HF Protocol, HF Study Report, Use-Related Risk Analysis, Justification for no HF Validation Study, Comparative Analysis, etc.); Other (specify): State the submission type if it is not one of the previous submission types listed above (e.g., formal dispute resolution request, REMS revisions). If this box is checked, provide the Reasons for the Submission in Field 27.

Field 22: SUBMISSION SUB-TYPE

Select one of the submission sub-types listed. See also 21 CFR 314.3(b).

Presubmission: Information submitted prior to the submission of a complete original application (e.g.,submission of partial application (rolling submission);

Amendment: A submission to a pending original application, or pending supplemental application, including responses to Information Request letters, Discipline Review letters, or other FDA communications. Amendments also include submissions that contain additional supportive material intended to augment or revise information previously submitted in a submission type listed under

Field 21 (e.g., amendment to an annual report);

Initial submission: A submission type under Field 21 that has never before been submitted (excluding presubmissions);

Resubmission: A complete response to an action letter, or submission of an original application that has been the subject of a withdrawal before FDA action or a refusal to file action.

Field 23: SUPPLEMENT CATEGORY

Select the appropriate type of supplemental application, if applicable.

CBE (Changes Being Effected): A supplemental application proposing certain changes for which distribution of the product made using the change(s) can occur upon FDA receipt of the application as described under 21 CFR 314.70(c)(6) and 21 CFR 601.12(c)(5);

CBE-30 (Changes Being Effected in 30 Days): A supplemental application proposing certain changes requiring submission at least 30 days prior to distribution of the product made using the change(s) as described under 21 CFR 314.70(c) and 21 CFR 601.12(c);

Prior Approval (PA): A supplemental application proposing a major change for which distribution of the product made using the change(s) cannot occur prior to FDA approval as described under 21 CFR 314.70(b) and 21 CFR 601.12(b).

Field 24: COMBINATION PRODUCTS

Field 21 (Submission Type) should be filled out before attempting to fill out Field 24. Field 24 is only fillable for original submissions and supplements (Labeling, CMC, Efficacy, REMS), including resubmissions and amendments to these types. Indicate if the product proposed within the submission is a combination product

(e.g., drug-device, drug-biological product, drug-device-biological product, see 21 CFR
3.2(e)) by selecting

'Yes' and entering the number below that best identifies the type:

1. Convenience Kit or Co-Package

2. Prefilled Drug Delivery Device/System

3. Prefilled Biologic Delivery Device/System

4. Device Coated/Impregnated/Otherwise Combined with Drug

5. Device Coated or Otherwise Combined with Biologic

6. Drug/Biologic Combination

7. Separate Products Requiring Cross Labeling

8. Possible Combination Based on Cross Labeling of Separate Products

9. Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)

If the product(s) in the submission is not a combination product, select 'No' and leave the Combination Product Type blank. If the submission relates to a drug product available in both combination product (e.g., pre-filled syringe presentation) and noncombination product (e.g., vial presentation) configurations) select 'Yes' and identify the type that applies to the combination product configuration. If the submission relates to a product configuration that has multiple combination product types (e.g., a submission is for a product that contains a prefilled syringe (Type 2) and is copackaged with other devices and drugs (Type 1)), select type '9'.

If this is the initial submission for a product for which a Request for Designation (RFD) was submitted, provide the six-digit RFD number. Field 25: Does the submission contain:

Only Pediatric data?: If the submission identified in Field 21 of this form contains data only from pediatric studies, select 'Yes'. If the submission does not contain data from pediatric studies, or is an original application or efficacy supplement that contains data from both adult and pediatric studies, select 'No'.

Digital Health Technology (DHT) Data?: If the submission contains Digital Health Technology

(DHT) data, select 'Yes'. DHTs are systems that use computing platforms, connectivity, software, and/or sensors, (e.g., activity trackers, mobile medical applications) for remote data acquisition from participants in a clinical investigation. Although not final, FDA's guidance on DHTs represents the Agency's current thinking on the use of DHTs: https://www.fda.gov/media/155022/download.

Field 26: PROPOSED MARKETING STATUS Select the appropriate Proposed Marketing Status. Field 27: REASONS FOR SUBMISSION

This section should contain a brief explanation of the contents of, or rationale for, the submission (e.g.,"manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of mm/dd/yy" or "pediatric exclusivity determination request" or "to fulfill a Subpart H postmarketing requirement").

If you selected 'Yes' for human factors information, specify what type of HF information is being submitted (e.g., HF protocol, HF study report, use-related risk analysis, justification for no HF validation study). If you selected 'Yes' for REMS Assessment Methods and Study Protocols, specify what type of methodologies and protocols are being submitted (e.g., survey methodologies, audit plans, drug use study, epidemiology studies).

Field 28: ESTABLISHMENT INFORMATION

If you selected 'Yes' for REMS Assessment Methods and Study Protocols, specify what type of methodologies and protocols are being submitted (e.g., survey methodologies, audit plans, drug use study, epidemiology studies). For original (initial) applications, efficacy supplements, CMC supplements, and resubmissions to these submission types, this section should include complete information on the locations of all manufacturing, packaging, and control sites for both drug substance and drug product. Establishment information on bioequivalence testing sites, excipient testing sites, and container/ closure manufacturing and testing establishments is not required in Field 28. For presubmissions and amendments to these submission types, complete establishment information should be provided in this section when applicable (e.g., an amendment that describes changes to previously submitted establishment information; an amendment that adds or removes an establishment; a presubmission that includes CMC information including establishment information).

For each site, please include the establishment name, address, registration (FEI) number, Master File (MF) or Drug Master File (DMF) number (for facilities used under a MF), and establishment DUNS number. Indicate whether or not the establishment is new to the application, if applicable. New establishments will have by default a 'pending' status. If it is not a new establishment, indicate its current status (e.g., active, inactive, or withdrawn) in the appropriate box.

For CMC and efficacy supplements indicate whether the establishment is involved in the change of the subject submission in Yes/No checkbox. Also provide the name, title (optional), address, phone number, fax number and email address for the contact at the site. In the section "Manufacturing Steps, and/or Type of Testing", provide a brief description of the specific manufacturing steps and/or type of testing (e.g., final dosage form, stability testing) conducted at the site (i.e., describe the type(s) of assays or testing completed). Indicate whether the site is ready for inspection, or if not, when it will be ready. Use the Continuation Page as needed. If continuation pages are not needed, click on the 'Remove Continuation Page' button at top/bottom of form.

Field 29: CROSS REFERENCES

This section should contain a list of all Biologics License Applications (BLAs),
Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Premarket Approval Applications (PMAs), Premarket Notifications (510(k)(s),

Investigational Device Exemptions (IDEs), and/or MFs/DMFs/Master Files for Devices (MAFs) that are cross- referenced in the current application. Use the Continuation Page as needed.

If continuation pages are not needed, click on the 'Remove Continuation Page' button at top/ bottom of form.

Field 30: This section contains items 1 through 20 which is a checklist that should be used to indicate the types of information contained within a particular application or submission. Check all that apply. A complete index or table of contents should immediately follow the Form FDA 356h and, if applicable, a User Fee Cover Sheet (Forms FDA 3397, 3792, or 3794). Note that the CFR references are provided for most items in order to indicate what type of information should or must be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency. Please note, selecting Field 30, item 15 indicates the complete Biological Products establishment description is included at Field 28.

Fields 31–38: CERTIFICATION

Enter the name and title, telephone number, facsimile number, email address, and street address of the applicant's Responsible Official in Fields 31–36 of the form. This person is responsible for certifying compliance with applicable laws and regulations. The authorized U.S. agent named in Field 6 of the form may also act as the applicant's Responsible Official.

The form must be signed in Field 37 by the applicant, or the applicant's attorney, agent, or other authorized official. 21 CFR 601.2(a). If the person signing the form in Field 37 does not reside or have a place of business within the United States, the form must be countersigned in Field 38 by an attorney, agent, or other authorized official who resides or maintains a place business within the United States. 21 CFR 314.50(a)(5).

CONCLUSION

The present thesis mainly discusses about the changes to approved nda and anda. On November 21, 1997, the Food & Drug Modernization Act (the Modernization Act) was enacted by Congress. Section 116 of the Modernization Act amended the Federal Food, Drug, and Cosmetic (FD&C) Act to add section 506A. This section outlines the requirements for making and reporting manufacturing changes to approved new drug applications (NDAs) and abbreviated new drug applications (ANDAs), as well as the requirements for distributing a drug product made with these changes. In order to comply with section 506A, the FDA then revised its regulations regarding supplements and other changes to an approved application (21 CFR 314.70).

In November 1999, FDA issued a guidance document entitled "Changes to an Approved NDA or ANDA." In April 2004, the Agency issues its first revision of the document, which takes the place of the original document (Nov. 1999). The guidance covers the Agency's recommendations for holders of NDAs and

ANDAs who are planning to make post approval changes (in accordance with section 506A). Types of Post Approval Changes:

If the holder of an NDA or ANDA is planning to make post-approval changes, they first need to specify the types of changes they'll make which fall under one of three categories: major, moderate, or minor.

1. Major Changes:

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 effectiveness of the drug product." A major change differs from the others in that it requires the submission of a *Prior Approval Supplement*, which must be approved by FDA prior to distribution of the drug product made using the change. Under certain circumstances, an applicant may ask the FDA to expedite its review of a prior approval supplement for public health reasons such as a drug shortage or if a delay in making the change would impose an extraordinary hardship on the applicant.

2. 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

3. Minor Changes

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 effectiveness of the drug product." There is no submission or supplement required for minor changes, the applicant must simply describe any minor changes that have been made in its next Annual Report that is submitted to the FDA.

BIBLIOGRAPHY

1. Changes to an Approved NDA or ANDA [Online] Available at: https://www.fda.gov/regulatory-information/search-fda-guidance- documents/changes-approved-nda-or-anda.

2. Lokesh M.S., N. Vishal Gupta, Bhushan Dinesh Belagoankar. Comparative Study of Process of Post Approval Change Application Submission and Approval for Marketing Authorization Variations in EU, US, India, Saudi Arabia and Singapore. International Journal of Drug Development and Research 2015 Jan;7(1):0975-9344.

3. Meyer MC. United States Food and Drug Administration requirements for approval of generic drug products. J Clin Psychiatry. 2001;62 Suppl 5:4-9; discussion 23-4.

4. Weisblatt H, Frezza C. Who to Sue and Where in ANDA Litigation: Personal Jurisdiction Post-Daimler. Food Drug Law J. 2014;69(3):351-64, i. PMID: 27382854.

5. Marzo A. Clinical pharmacokinetic registration file for NDA and ANDA procedures. Pharmacol Res. 1997 Dec;36(6):425-50. doi: 10.1006/phrs.1997.0254.

6. Nagori BP, Mathur V, Garg S. Generic drug approval: a US perspective. Curr Med Res Opin. 2011 Mar;27(3):541-5. doi: 10.1185/03007995.2010.548374.

7. ANDA [Internet], Available from: https://www.fda.gov/drugs/new-drugs-fdacders- new-molecular-entities-and-new-therapeutic-biological-products/newdrug- therapy-approvals-2019

8. Requirements and Resources for Approved ANDAs. Available from: https://www.fda.gov/drugs/abbreviated-new-drug-applicationanda/requirements- and-resources-approved-andas

9. Hatch-Waxman Act [Internet], Available from: https:/ /www.everycrsreport .com/files /20160928_R44643_1c2fafad2efe96d4c0fe4 4f2f 23308dcfc 059f83.pdf

10. Code of federal regulation title 21 CFR 314.70 [online] Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=31 4. 70

11. Balasubramanian et al. Supac: A Regulatory Approach for High Quality Documentation in Chemistry, Manufacturing and Control (CMC). World Journal of Pharmacy and Pharmaceutical Sciences. Volume 7, Issue 5, 437-452

12. Rahulgiri Goswami, Dr. Dilip Maheshwari. Comparative Study of Regulatory Requirements for Post-Approval Changes in US, Europe and South Africa. JPSBR: Volume 4, Issue 1: 2014 (177-183)

13. Manufacturing Site Change Supplements: Content and Submission [online] Available at: https://www.fda.gov/regulatory-information/search-fda-guidance- documents/manufacturing-site-change-supplements-content-and-submission
https://en.wikipedia.org/wiki/Specification_(technical_standard)

14. Code of federal regulation title 21 CFR 314.105 [online] Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.105

15. IRA RB, Robert PM. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare;2008. p. 46-48.

16. Rick NG. Drugs from discovery to approval.2nd ed. John Wiley & Sons, Inc.; 2008. p. 212-220.

17. IRA RB, Robert PM. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare;2008. p. 49-51.

18. Clinical Trial & Global Clinical Trial[Internet].[cited 2014 January].Available from: http://cdsco.nic.in/clinical_trial.htm.

19. The New Drug Approval Process[Internet].[cited 2014 January].Available from:http://www.fda.gov/cder/handbook.

20. CDER Guidance: cited 2014 Available from: www.fda.gov/cder/regulatory/applications/ind_ page_1.htm.

21. Guidance for industry on preparation of common technical document for import/manufacture and marketing approval of new drugs for human use. (NEW DRUG APPLICATION–NDA) [Internet].[cited 2014 January].Available from: http://cdsco.nic.in/CTD_Guidance%20-Final.pdf

22. U.S. Government Printing Office, 2010, Title 21, Volume 7, Code of Federal Regulations: 21 CFR § 601.2: Requests for samples and protocols; official release, U.S., GPO, Washington, DC.

23. EC, 2008, Commission Regulation (EC), Number (No) 1234/2008 of 24 November 2008 concerning the examination of variations to the term of marketing authorization for medicinal products for human use and veterinary medicinal products, Offical Journal of European Union, Brüssel.

24. European Parliament and of the Council; 2004, Regulation (EC), No 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

25. U.S. Government Printing Office, 2010, Title 21, Volume 5, Code of Federal Regulations: 21 CFR § 314.81: Other postmarketing reports, U.S. GPO, Washington, DC.

26. U.S. Government Printing Office, 2010, Title 21, Volume 7, Code of Federal Regulations: 21 CFR § 601.12 (a): Changes to an approved application, U.S., GPO,Washington, DC.