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# CMC-POST APPROVAL MANUFACTURING CHANGES TO BE DOCUMENTED IN ANNUAL REPORTS DATLA NIKHILA, AMEENPALLI BHAVANA, Y Sarah sujitha

**M PHARMACY**

**Krishna Teja pharmacy college**

## ABSTRACT

CMC is an acronym for chemistry, manufacturing, and controls which are crucial activities when developing new pharmaceutical products. CMC involves defining manufacturing practices and product specifications that must be followed and met in order to ensure product safety and consistency between batches. Chemistry, Manufacturing and Controls (CMC) of a medicinal product is the body of information that defines not only the manufacturing process itself but also the quality control release testing, specifications and stability of the product together with the manufacturing facility and all of its support utilities, including their design, qualification, operation and maintenance. This describes chemistry, manufacturing, and controls (CMC) post approval manufacturing changes that FDA generally considers to have a minimal potential to have an adverse effect on product quality. Under FDA regulations, post approval changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on product quality must be documented by applicants in an annual report.

## INTRODUCTION

CMC is an acronym for chemistry, manufacturing, and controls which are crucial activities when developing new pharmaceutical products. CMC involves defining manufacturing practices and product specifications that must be followed and met in order to ensure product safety and consistency between batches.

Chemistry, Manufacturing and Controls (CMC) of a medicinal product is the body of information that defines not only the manufacturing process itself but also the quality control release testing, specifications and stability of the product together with the manufacturing facility and all of its support utilities, including their

design,qualification, operation and maintenance.

CMC regulatory affairs and compliance is seen as a process of governance which ensures CMC practices are carried out in agreement with regulatory agencies requirements and expectations. Since such requirements and expectations change with time, a function of CMC regulatory compliance is to ensure that all CMC practices are updated accordingly.

CMC regulatory compliance ensures that, if the pharmaceutical organization has made any CMC-specific commitment to regulatory agencies, either verbally or in writing, such CMC practices are carried out.

Within the EU, the marketing authorization holder and Qualified Person will be held responsible if the manufacture of a medicinal product is not undertaken according to the details supplied in the CMC section (CTD, Module 3 or equivalent) of the approveddossier.

The legal framework in the EU is defined in Directive 2001/83/EC, as amended, with key statements found within Articles 20, 23 and 51. Similar principles apply to the US and other international markets.

If a marketing authorization holder has a product which is not manufactured, packed, tested or as stable as described in the information supplied to the relevant national

authority, then the MA is considered to be in non-compliance with manufacturing procedure.

The consequences of non-compliance can range from having to rectify the differences under the scrutiny of the relevant national authority, to fines, withdrawal of the marketing authorization, or the suspension of product distribution on a national or regional level.

Many companies that find a level of regulatory non-compliance within their manufacturing organization will possibly identify the principal cause to be a lack of robustness in their change control system stretching from the manufacturing quality organization to the regulatory affairs functions at manufacturing, corporate and country-based local regulatory functions.

If the change control system lacks robustness, and clarity in responsibility definition for post-approval actions, changes made at manufacturing level can get overlooked and result in manufacturing details and CMC-registered details being out of sync.

Given the possible consequences of non-compliance, which include damage to the reputation of the whole company, it is best to prevent non-compliance issues from developing initially by strengthening the change control system and company infrastructure in CMC pharma.

If a company as a marketing authorization holder has a portfolio of products where it is suspected there may be divergence between registered CMC details and manufacturing practice, due action should be taken to start or continue a compliance program to identify and rectify compliance issues.

The consequences of an external body identifying non-compliance within an organization and the damage to

the company's reputation will be mitigated if a company is already engaged in a thorough, continuous and well-structured compliance program.

Before initiating a compliance program, it is always best to define the scope of the program and assign enough resources to it. The compliance program can range from

preparing single marketing authorization in a single country for license renewal, all the way to include a section of the company portfolio or full portfolio in multiple countries.

It is also important to identify clearly the decision-makers, and agree on and define the roles and responsibilities from the beginning, as a compliance program will likely require difficult decisions to be made. Any project of this nature must include the quality organization and specifically the (EU) Qualified Persons (or equivalent) responsible for the release to market of the products in its scope.

Within a CMC pharma, the measurement of compliance can give rise to conflicts of interest, as the results can be seen as a measure of a function's performance. One possible option to avoid this aspect, and ensure a level of impartiality, is to use a suitably experienced regulatory outsourcing provider for critical parts of the project.

In conclusion, organizations that find a level of regulatory non-compliance within their manufacturing organization may identify the principal cause to be a lack of robustness in their change control system. Building robustness also needs senior management to be in agreement about any process change strategy and enabling implementation teams at the ground level to have the authority to drive remediation programs to completion.

**Post approval changes:** These are the non-avoidable changes due to the many reasons for improving products quality and safety. According to US-FDA the changes which are made after the approval of the product are supposed to be reported as major, moderate and minor changes based on the impact on the process and filings.

Or

Variation/Post-Approval Change A change to any aspect of a pharmaceutical product, including but not limited to change in the method and site of manufacture, specifications for the finished pharmaceutical product and ingredients, container, labeling and product information.

Under 21 CFR 314.70, all post approval CMC changes beyond the variations provided for in an approved NDA and ANDA are categorized into one of three reporting categories: major, moderate, or minor.

A Post-Approval Study is exactly what it sounds like: a study that is carried out after FDA has approved your device to be placed on the US market. It's used to provide more evidence for the safety and effectiveness of your device after it's been approved.

Any Marketing Authorization Holder (MAH) of a pharmaceutical product may apply for PAC, provided that:

The MAH has a valid License to Operate (LTO); and

The pharmaceutical product has a valid Certificate of Product Registration(CPR).

B. Classification

All PACs shall be based on the latest version of the ASEAN Variation

Guidelines and country-specific regulations. The list of PACs with their correspondingcodes and classifications shall be included in the Philippine

Variation Guidelines, which shall be updated whenever the adopted guidelines andregulations have been revised.

ASEAN Variation Guideline for Pharmaceutical Products

a. Major Variation

b. Minor Variation

i. Prior Approval

ii. Notification

Country-Specific Guideline for Post-Approval Changes to PharmaceuticalProducts

Major Variation

Minor Variation

i. Prior Approval

ii. Notification

FDA reserves the right to correct the filed categorization of PAC application, where deemed necessary, according to the set guidelines. This may render the application unsatisfactory, wherein an appropriate response 4 will be issued by the Office, and the MAH shall be required to submit a new application under a new Document Tracking Number (DTN).

To the holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding the types of changes to be documented in annual reports.

Specifically, the guidance describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that we have determined will likely have a minimal potential to have an adverse effect on product quality2 and, therefore, should be documented by applicants in an annual report.3,4

Appendix A lists examples of CMC postapproval manufacturing changes previously submitted under manufacturing supplements that we have determined generally to be of low risk to product quality. Appendix B provides examples of minor changes to be documented in an annual report that were previously published

in FDA's Scale-up and Postapproval Changes (SUPAC) guidances and other postapproval change CMC guidances.

This guidance provides recommendations to holders of approved new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), and abbreviated new animal drug applications (ANADAs) and holders of drug master files (DMFs) and veterinary master files (VMFs) who want to make a change to the drug substance manufacturing process during the drug product application's postapproval period. It does not address holders of biologics license applications (BLAs) or holders of any master files cross22 referenced in BLAs. The guidance applies to synthetic drug substances and the synthetic steps involved in preparing semisynthetic drug substances. The guidance covers the following changes: • Facility, scale, and equipment changes associated with all steps of drug substance manufacturing.

Specification changes to starting materials, raw materials, intermediates, and theunfinished and final drug substance.

Synthetic manufacturing process changes.

Changes in the source of the drug substance.

Changes to the container closure system for the drug substance.

**MANUFACTURING PROCESS CHANGES**

This category encompasses a wide range of process-related changes, such as a change in the route of synthesis or an addition of a reprocessing procedure. Changes to the manufacturing process at or after the final solution step are considered to have a high potential to adversely affect the impurity profile and physical properties of the drug substance. New specifications may be needed when new solvents, reagents, starting materials, or intermediates are involved in a change to the manufacturing process. (See also section VII).

When the process changes involve concurrent facility, scale, or equipment changes (e.g., changing the method of isolating the drug substance from filtration to centrifugation, changing from tray to fluid bed drying), the changes are considered a multiple change (see section XI)

A. Changes That Do Not Involve the Route of Synthesis

Examples include the following types of changes that might be made in one or more steps of the synthetic procedure, in purification processes, or in reprocessing operations:

Changes in unit operations (e.g., addition, deletion, change in the order, orrepetition of an existing unit operation on a routine basis).

Addition or deletion of raw materials (e.g., solvents, reagents) or ancillarymaterials (e.g.,resins, processing aids).

Changes in solvent composition.

Changes to process parameters (e.g., temperature, pH, reagent stoichiometry, time).

Documentation of equivalence is recommended for most, but not all, cases. For example, if the amount of charcoal used in a process increases, equivalence testing may not be warranted. However, if the amount of charcoal decreases, there is the possibility of an increase in impurities; therefore, equivalence testing should be performed.

B. Changes in Route of Synthesis in One or More Steps

In general, changes in route of synthesis are considered to have a moderate to high potential to adversely affect the impurity profile of the drug substance. The manufacturing process should be validated using the new route of synthesis. Impurity carryover studies and spike/purge studies should be conducted as appropriate. Control of mutagenic impurities in or expected to be in the final drug substance should be evaluated according to ICH M7

C. Establishing a Reprocessing Procedure as Part of the Established Manufacturing Process

Reprocessing is not considered a routine event. If frequent reprocessing is expected, the procedures should be included as part of the established manufacturing process described in an application. If an application is approved without reprocessing procedures in the manufacturing process, the procedures can be added postapproval as an amendment to the DMF or as a supplement to the NDA or ANDA. Establishing a reprocessing operation as part of the manufacturing process has a low potential to adversely affect the physical properties of the drug substance. This category does not cover the addition of new steps beyond the established manufacturing process, which is considered reworking. Reworking increases the potential to affect the drug substance properties and needs more evaluation and testing according to ICH Q7.

D. Recommended Documentation for the Drug Substance in a Master File or anApproved Application

For changes involving the manufacturing process, submissions to master files and the drug substance section of approved applications should include the following documentation:

A description of and rationale for the proposed change.

Specifications for new materials (e.g., starting materials, reagents, solvents, intermediates) as well as representative COAs. If new specifications are necessary in conjunction with a process change, this would be considered a multiple change

Executed batch records should be provided for master files referenced in support of an ANDA application.

Evaluation of the impurity profile (for intermediates or drug substance) and physicalproperties (for drug substance), including:

A comparison of the impurity profile of pre- and post-modification material to establish equivalence as described in section IV, Assessment of Change. Historical data for comparison may be submitted, if

applicable, along with a description of the source of the historical data. Data and COAs from at least three consecutive batches of the material manufactured using the alternate manufacturing process should be provided. These data may be for intermediates or drug substances depending on which part of the manufacturing process is being modified.

A description of new or revised analytical procedures that are used for the intermediate or drug substance analysis to evaluate the presence or absence of impurities. If the analytical procedure is used for drug substance testing, a summary of validation/verification data should be provided for new or revised methods and for existing methods if their use is being extended beyond their original purpose.

If an intermediate specification change is a result of the process change that introduces the use of a new reagent, solvent, catalyst, or raw material, and such change will not result in a change in drug substance specification, data to justify test exclusion for new impurities as the result of the change.

Carryover studies that were conducted to justify upstream control of impurities should be repeated if applicable to the portion of the process being changed.

If the impurity profile is demonstrated to be equivalent in an intermediate or in the drug substance, the submission should include:

An evaluation of the impurities in the pre- and post-modification material and a discussion of purging data or the results from spike/purge studies.

A commitment to put the first commercial-scale batch of the drug substance intothe stability program.

If impurity profile equivalence is not demonstrated in an intermediate or in the drug substance and a revised or new in-process control or specification is proposed.

If the drug substance impurity profile or physical properties are not equivalent, then 3 months of accelerated and 3 months of long-term stability data from three batches should be provided in the drug substance should also be included. If the changes involve the route of synthesis, the submission should contain additional information, which includes but is not limited to:

A detailed description of the new synthetic procedures, including the operating conditions, controls of critical steps, and intermediates.

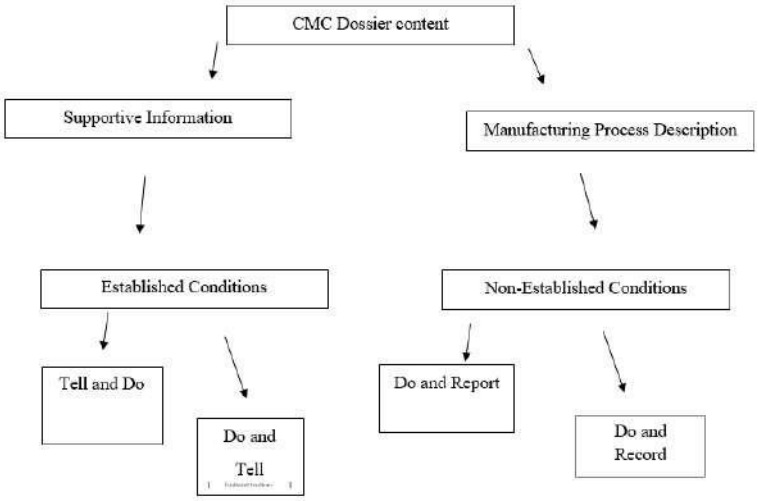



**Fig:**

Continuous pharmaceutical manufacturing offers potential flexibility, quality, and economic advantages over batch processing, both in process development and manufacturing for the pharmaceutical sector.

Over the past decade, there have been significant advancements in science and engineering to support the implementation of continuous pharmaceutical manufacturing. These investments, along with the adoption of the QbD-Quality by design for pharmaceutical development and the advancement of PAT for designing, analyzing, and controlling manufacturing, have progressed the scientific and regulatory readiness for continuous manufacturing. Building on this progress, research efforts should continue in several key areas to address the remaining implementation challenges.

# REVIEW OF LITERATURE

US FDA guidance provides recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding the types of changes to be documented in annual reports. Specifically, the guidance describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that we have determined will likely have a minimal potential to have an adverse effect on product quality and, therefore, should be documented by applicants in an annual report.[1]

QbD developments, shelf life of drug products, and PMC were surveyed in the review reports of the US Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA) websites. Overall, 86% of BTD products and two out of three Sakigake products were developed using a QbD approach. Furthermore, 92% of BTD products and two out of three Sakigake products were granted a shelf life of at least 18 months. In the BTD pathway, 50% of PMCs concerned the reevaluation of specification and test method. For most BTD and Sakigake products, the control strategy was developed utilizing the QbD concept, and long shelf life was granted despite the accelerated timeline. No discount for specification setting was observed for assuring quality, based on the available data at the time of approval in the BTD and Sakigake programs, although PMCs were mainly required for reevaluation of the specification and test method in BTD programs. Further efforts should focus on creating/revising guidelines for CMC development.[2]

Approval letters issued by the FDA between 2017-2020 for oncology drugs were systematically analyzed for PMRs or PMCs with requests for RWE. For each PMR/PMC identified, the characteristics of the approvals, the PMRs/PMCs, and the RWE requested were reviewed. Of 189 oncology drug approvals with 456 associated PMRs/PMCs, a total of 15 PMRs/PMCs specified RWE. Compared with all oncology drug approvals, the 14 approvals with PMRs/PMCs requesting RWE were more frequently accelerated approvals, for new therapies, with orphan indications. All 15 PMRs/PMCs requested real-world safety data, with 3 also requesting real-world effectiveness data. RWE requested included post-marketing safety reports, prospectiveobservational studies, expanded access study data, and registry data. As a greater proportion of safety and efficacy data generation for oncology drugs shifts to the post- marketing setting, RWE has the potential to become an integral component of PMR/PMC fulfillment.[3]

FDA guidance to describe the evolution of laws and standards affecting drug testing, the use of new approval programs and standards, expansions of the role and authority of the FDA, and changes in the number of drugs approved from the 1980s to 2018. Sources of evidence included principal federal laws and FDA regulations (1962- 2018) and FDA databases of approved new drugs (1984-2018), generic drugs (1970- 2018), biologics (1984-2018), and vaccines (1998-2018); special development and approval programs (Orphan drug [1984-2018], Fast-Track [1988-2018], Priority Review and its predecessors [1984-2018],

Accelerated Approval [1992-2018], and Breakthrough Therapy [2012-2018]); expanded access (2010-2017) and Risk Evaluation and Mitigation Strategies (2008-2018); and user fees paid to the FDA by industry (1993-2018).[4]

The following four FDA programs are intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation (see section IV for an overview of the programs). The purpose of this guidance for industry is to provide a single resource for information on FDA's policies and procedures for these four programs as well as threshold criteria generally applicable to concluding that a drug is a candidate for these expedited development and review programs.[5]

The US Food and Drug Administration (FDA) is a scientific, regulatory, and public health agency whose authority includes overseeing the marketing of products relevant to medical practice. Devices are classified based on the extent of oversight needed to ensure public safety. Divisions within the FDA provide specific expertise regarding drugs, devices, biologic products, and combinations thereof. Various pathways exist to apply for marketing through the FDA, depending on the nature of the product and its intended use. Expert panels advise the agency on issues related to product safety and efficacy, and clinical studies may be required to provide data based on thesparameters. Clinical data are monitored postapproval for potential adverse events not evident in earlier trials. Orthopaedic surgeons are involved in all aspects of the FDA as employees, consultants, product advocates, participants in clinical trials and advisory panels, and experts involved in the appropriate reporting of adverse events.[5]

The changes introduced by the Medical Device User Fee and Modernisation Act should ensure a timely and effective review process. The impact of some of the reforms is discussed here.[6]

After expending considerable effort to comply with United States (US) marketing authorisation regulations, a company launched its first product on the US market. Unfortunately, the company failed to comply with other applicable US regulations, which led to a delay in the US product introduction and FDA postmarketing enforcement actions against the product. This article discusses ways that companies can prevent this from happening.[7]

Postmarketing Study Commitments (PMCs) are, most commonly, agreements made by pharmaceutical companies at the time of an FDA approval to perform a study or studies to elucidate further characteristics of the drug under consideration. The role of PMCs in drug regulation has come under considerable scrutiny in recent years, particularly as discussions of drug safety have intensified. Although these agreed-upon PMCs are described in FDA regulations, such PMCs are not sought by FDA with every approval, and completion of the agreed-upon studies is not a requirement for the drug's sponsor (there are required PMCs under certain

regulatory provisions and these are discussed below). Requests by FDA at the time of regulatory approval for studies under PMCs have been a common practice for many years. When made, PMCs are described in the approval letters and are therefore publicly available. Concerns over whether PMCs were being duly performed, reported, and reviewed by FDA were addressed in the FDA Modernization Act of 1997, which required more detailed reporting by manufactures on their progress in meeting the PMCs and required FDA to report certain information publicly.[8]

The United States Food and Drug Administration (FDA) is charged with assuring the safety and effectiveness of a variety of medical products and the FDA's Center for Devices and Radiological Health is responsible for premarket and postmarket regulation of medical devices. In this paper, we review--from device classification and clinical studies to the final marketing application--FDA's premarket requirements and postmarket requirements as they relate to deep brain stimulation devices.[9]

This paper provides an overview of the United States Food and Drug Administration's (FDA) role as a regulatory agency in medical device clinical studies involving human subjects. The FDA's regulations and responsibilities are explained and the device application process discussed. The specific medical device regulatory authorities are described as they apply to the development and clinical study of retinal visual prosthetic devices. The FDA medical device regulations regarding clinical studies of human subjects are intended to safeguard the rights and safety of subjects. The data gathered in pre-approval clinical studies provide a basis of valid scientific evidence in order to demonstrate the safety and effectiveness of a medical device. The importance of a working understanding of applicable medical device regulations from the beginning of the device development project is emphasized particularly for novel, complex products such as implantable visual prosthetic devices.[10]

Policy Points Food and Drug Administration (FDA) advisory committee recommendations and the agency's final actions exhibit high rates of agreement, with cases of disagreement tending to reflect the proposed action type and degree of advisory committee consensus. In the case of disagreements, the FDA tended to be less likely than its advisory committees to approve new products, approve new supplemental indications, or enact new safety changes. These findings raise important issues regarding the factors that differentially shape decision making by advisory committees and the FDA as an agency, including institutional or reputational concerns.[11]

This analysis sought to quantify voting behavior and other characteristics of advisory committee (AC) meetings and compare that with the U.S. Food and Drug Administration's (FDA) approval decisions from 2010 to 2015. The analysis of the Center for Drug Evaluation and Research AC meetings was conducted using publicly

available information from the FDA website and the sponsors' websites. There were 163 voting sessions,

207 votes, and 229 meetings. Voting questions assessed approval (63%), acceptable risk-benefit profile (19%), efficacy (8%), safety and efficacy (7%), and safety (3%). The AC voted in favor of approval 67% of the time and against approval 33% of the time, although it heavily favored one outcome when voting favorably or unfavorably. The FDA approval decision supported the committee's decision in 90% of cases. When such agreement did not occur, it was due to differences in clinical opinion (43%), manufacturing deficiencies (14%), lack of manufacturing data (14%), and a post-AC event (5%). There was insufficient information to determine why there was a differing opinion in 24% of cases. When FDA had a differing opinion, the agency typically did not approve a substance in which the committee recommended approval (81%). The results support past research examining the topic from 2001 to 2010. Voting patterns were relatively constant, and they generally heavily favored one outcome. The FDA's ultimate approval decision was in line with the AC vote the vast majority of cases. Any disagreement was usually due to FDA having a differing opinion regarding clinical importance, furthering the notion that AC insight is heavily considered but not the final determinant in agency action. This topic has importance in understanding pharmaceutical approval in the United States, and this has clinical practice implications.[12]

## AIM AND OBJECTIVE

The aim and objective of the present work is to provide recommendations to holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding the types of changes to be documented in annual reports. Specifically, the guidance describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that we have determined will likely have a minimal potential to have an adverse effect on product quality and, therefore, should be documented by applicants in an annual report.

FDA differentiates post-approval changes into four categories: major changes requiring the submission of a prior approval supplement (PAS); moderate, requiring the filing of changes being effected-30 days supplement (CBE-30), or a CBE-0 supplement; or minor changes requiring only the filing of an annual report. Annual reports do not need to be submitted as supplements.

This work also focus on Changes in an approved application to allow for the use of a different facility or establishment, including a different contract laboratory, normally require FDA approval before the change is made (21 CFR 314.70(b)). FDA regulations at 21 CFR 314.70(a) provide that applicants may make changes to an approved application in accordance with a guidance, notice, or regulation published in the Federal Register that provides for a less burdensome notification of the change (e.g., by notification at the time a supplement is submitted or in the next annual report). This document provides guidance on a less burdensome approach to providing notice (i.e., Changes Being Effected (CBE) supplement) of certain postapproval changes within themeaning of 314.70(a)

# DISCUSSION

## CONTENTS OF ANNUAL REPORT NOTIFICATION

To document changes in an annual report in accordance with 21 CFR 314.81(b)(2)(iv)(b) and

314.70(d)(3), the applicant must include a full description of the CMC changes that were made that the applicant believes did not require a supplemental application under sections 314.70(b) and (c). This description should include:

- A list of each change and the date each change was implemented; and
- Relevant summary of data from studies and tests performed to assess the effects of each change on product quality, including (where applicable) a list of cross- references to change control and change validation protocols and standard operating procedures (SOPs) that were used to assess or demonstrate the effect of the change.

The description also should include:

- The name(s) of one or more drug products affected or involved in the change(e.g., different label strengths/product presentations); or
- Reference to any previously approved grouped supplements if the changeaffected multiple products.

Executed batch records, SOPs, and data from studies and tests performed to assess theeffects.

## PAPERWORK REDUCTION ACT OF 1995

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 (44

U.S.C. 3501-3520). The expiration of the OMB control number will be updated periodically.

The total number of supplements submitted per year is estimated to reduce based on the recommendations in the guidance because certain changes submitted as supplements would now be documented in annual reports. Therefore, for such changes, the information collection with respect to the submission of supplements will be reduced. Because the number of supplements per year is estimated to reduce, the total number of hours for preparing supplements would correspondingly reduce. Send comments regarding this burden estimate or suggestions for reducing this burden to:

The Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 4178, Silver Spring, MD20993-0002.

This guidance also refers to previously approved collections of information found in FDA regulations:

(1) The submission of supplements to FDA for certain changes to an approved application in accordance with 21 CFR 314.70 and 314.71;

(2) The submission of annual reports to FDA (Form FDA 2252) in accordance with § 314.81(b)(2);

(3) The submission of supplements to an approved ANDA for changes that require FDA approval; and

(4) Other post- marketing reports for ANDAs in accordance with § 314.98(c), of which the estimate for annual reports is included under § 314.81(b)(2).

**APPENDIX A:** EXAMPLES OF CMC POSTAPPROVAL MANUFACTURING CHANGES TO BE DOCUMENTED IN ANNUAL REPORTS IF THEY HAVE A MINIMAL POTENTIAL TO HAVE AN ADVERSE EFFECT ON PRODUCT QUALITY

**1. Components and Composition**

1.1. Elimination or reduction of an overage from the drug product manufacturing batch formula that was previously used to compensate for manufacturing losses.

1.2. Change in coating formulation for immediate-release solid dosage forms if the coating material and quantity have been approved for another similar product and the change does not alter release of the drug, specification (i.e., tests,analytical procedures, and acceptance criteria for test results), or stability.

1.3. In instances where the supplier of an inactive ingredient was specified in an approved application, change to a new supplier of that inactive ingredient (e.g., change from one drug master file (DMF) holder to other DMF holder or change to a new qualified supplier). This is applicable only if the inactive ingredient's specification remains unchanged.

**2. Manufacturing Sites**

2.1. Minor structural modifications made in the sterile product manufacturing facility approved in an application that do not affect a product manufacturing area or sterility assurance and do not change product quality or specification.

2.2. In the manufacturing of sterile products, the addition of barriers within a conventional fill area to prevent routine in-process human intervention in an existing filling or compounding area that is qualified and validated by established procedures.

**3. Manufacturing Process, Batch Size, and Equipment**

3.1. The following process changes:

3.1.1. Addition of a sieving step(s) for aggregates removal if it occurs under nonaseptic conditions.

3.1.2. Changes in mixing times (for blending powders, granules) for immediate- release solid oral do3.2. Manufacturing batch size or scale change that results from combining previously separated batches (or lots) of in-process material to perform the next step in the manufacturing process if all combined batches meet the approved in-process control limits, the next step remains unaffected, and appropriate traceability is maintained.

3.3. For equipment used in aseptic manufacturing processes (e.g., new filling line, new lyophilizer), replacement of equipment with that of the same design and operating principle, when there is no change in the approved process methodology or in-process control limits.

3.4. Addition of identical processing lines that operate parallel to each other in the drug substance and drug product manufacturing process with no change in in- process control limits or product specification.

3.5. For sterile drug products, addition of, deletion of, or change in a reprocessing protocol for refiltrations to control bioburden because of filter integrity test failures.

3.6. Decrease in the number of open handling steps or manual operation procedures, when it reduces risk to product and there is no other change to the process (e.g., implementation of aseptic connection devices to replace flame protection procedures).

3.7. For sterile drug products, changes to the ranges of filtration process parameters (such as flow rate, pressure, time, or volume, but not pore size) that are within currently validated parameters ranges and therefore would not warrant newvalidation studies for the new ranges.

3.8. In the manufacture of sterile drug products, change from a qualified sterilization chamber (ethylene oxide (EtO), autoclave) to another of the same design and operating principle for the preparation of container/closure systems, sterilization of “change parts” for processing equipment, and terminal sterilization of product, when the new chamber and load configurations are validated to operate within the previously validated parameters. This does not include situations that change the validation parameters.

**4. Specifications**

4.1. Addition of a new test to the specification for an excipient

4.2. Change to the specification for a drug substance, drug product, or pharmacopeial excipient that is made to comply with the official compendia if it is a change that does not relax an acceptance criterion or delete a test.

Specification changes not suitable for documentation in an annual report include changes to an assay, tests for impurities, degradation products, product-related substances, or biological activities that are approved in NDAs and ANDAs. Suchchanges should be submitted in a supplement.

4.3. Change in the approved analytical procedure if the revised method maintains the original test methodology and provides equivalent or increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it claims to have or is represented to possess and the acceptance criteria remain unchanged (e.g., change in the flow rate or sample preparation for a high-performance liquid chromatography (HPLC) method).

4.4. Replacement of a nonspecific identity test with a discriminating identity test that includes a change in acceptance criteria.

4.5. Addition of an in-process test.

4.6. Replacement of blend uniformity and in-process homogeneity tests with other appropriate testing that ensures adequacy of mix.

4.7. Revision of tablet hardness (e.g., acceptance criterion for test result or change to a different analytical procedure and its associated acceptance criterion for test result) if there is no change in the approved dissolution analytical procedure, criteria, or associated dissolution profile.

4.8. Addition of a test for packaging material to provide increased assurance of quality.

4.9. Tightening of an approved acceptance criterion for a drug substance, a drug product, drug product formulation components, and in-process material.

**5. Container/Closure System**

5.1. A change in the container/closure system for the storage of a nonsterile drug

substance (solid, semisolid, or liquid) when the proposed container/closure system has no increased risk of leachable substances in the extractable profile (for semisolids and liquids) and equivalent protection properties for the packaged material.

5.2. Use of or transfer to a contract manufacturing organization (CMO) for the washing, drying, or/and siliconization of a drug product stopper or any part of a container closure system, provided the applicant certifies that the CMO's processes have been validated and the CMO's site has been audited and found CGMP compliant by the applicant (or by another party sponsored by the applicant).

5.3. For solid oral dosage forms, when the change is to use another suitable primary packaging component used in any other CDER-approved drug product.

5.4. For parenteral drug products, a change in glass supplier without a change in glass type or coating and without a change in container/closure dimensions

5.5. Changes to a crimp cap (ferrule and flip cap/overseal), provided that there are no changes to the color and that the container and closure integrity have been demonstrated using a validated test method. Note, however, that a change in the flip cap/overseal color to make it consistent with an established color coding system for that class of drug products is to be documented in an annual report.

5.6. Change to delete the company trademark or other markings on the crimp cap (ferrule and flip cap/overseal) to comply with the official compendium.

**6. Labeling Changes**

6.1. Revision in drug product labeling to reflect the qualitative change in inactive ingredient(s) of coating formulation, as recommended in 1.2 above. The final Structured Product Labeling (SPL) reflecting the qualitative change should be submitted to the Agency when implementing this change to allow for maintenance of the current product information in eLIST.12 This will help ensure the safe and effective use of the drug product.

6.2. A change in the drug product labeling to revise information related to CMC changes discussed in this guidance. If the change involves associated revision ofdrug product labeling, 6.1 above would apply.

**7. Miscellaneous Changes**

7.1. Extension of the drug substance retest dating period or drug product expiration dating period based on real-time stability data from pilot-scale or larger/commercial-scale batches following an approved stability protocol.

7.2. For immediate release solid oral dosage forms, if a dissolution test is performed, elimination of a test for identity or hardness from an approved stability protocol.

**APPENDIX B: EXAMPLES OF CHANGES TO BE DOCUMENTED IN AN ANNUAL REPORT FROM FDA'S SUPAC-IR, SUPAC-MR, SUPAC-SS, AND CHANGES TO AN APPROVED NDA OR ANDA GUIDANCES**

**SUPAC-SCALE UP POST APPROVAL CHANGES**:

During the postapproval period, to change:

1) The components or composition;

2) The site of manufacture;

3) The scale-up/scale-down of manufacture; and/or
4) The manufacturing (process and equipment) of an immediate release oral formulation.

The guidance defines:

1) Levels of change;

2) Recommended chemistry, manufacturing, and controls tests for each level of change;

3) In vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and

4) Documentation that should support the change. For those changes filed in a changes being effected supplement‖ [21 CFR 314.70(c)], the FDA may, after a review of the supplemental information, decide that the changes are not approvable. Thus sets forth application information that should be provided CDER to assure continuing product quality and performance characteristics of an immediate release solid oral dose formulation for specified postapproval changes.

**FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS: COMPONENTS AND COMPOSITION**

This section of the guidance focuses on changes in excipients in the drug product. Changes in the amount of drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a newexcipient or deleting an excipient are defined at Level 3 (defined below), except as described below.

**A. Level 1 Changes**

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

**Examples:**

a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.

b. Changes in excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:the total additive effect of all excipient changes should not be more than 5%

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and stability testing. Stability testing: onebatch on long-term stability data reported in annual report.

b. Dissolution Documentation

None beyond application/compendial requirements.

c. In Vivo Bioequivalence Documentation None.

3. Filing Documentation

Annual report (all information including long-term stability data).

**B.** Level 2 Changes

1. Definition of LevelExamples:

a. Change in the technical grade of an excipient. (Example:Avicel PH102 vs. Avicel PH200.)

b. Changes in excipients, expressed as percent (w/w) of total formulation, greater than those listed above for a Level 1 change but less than or equal to the following percent ranges (which represent a two fold increase over Level 1 changes):

The total additive effect of all excipient changes should not change by more than 10%.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and batchrecords. Stability testing: 1 batch with 3 months accelerated stability data in supplement and 1 batch on long-term stability.

b. Dissolution Documentation

Case A: High Permeability, High Solubility Drugs

Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C (below).

Case B: Low Permeability, High Solubility Drugs Multi-point dissolution profile should be performed in the application/compendia medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

Case C: High Permeability, Low Solubility Drugs

Multi-point dissolution profiles should be performed in water, 0.1 N HCl, and USP Buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used product formulations should be similar.

c. In Vivo Bioequivalence Documentation

None: if the situation does not meet the description in Case A, Case B or Case C,

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

**C.** Level 3 Changes

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. Tests and filing documentation vary depending on the following three factors: therapeutic range, solubility, and permeability.

Examples:

a. Any qualitative and quantitative excipient changes to a narrow therapeutic drugbeyond the ranges noted in SectionIII.A.1.b.

b. All other drugs not meeting the dissolution criteria under Section III.B.2.b.

c. Changes in the excipient ranges of low solubility, low permeability drugsbeyond those listed in Section III.A.1.b.

d. Changes in the excipient ranges of all drugs beyond those listed in SectionIII.B.1.b.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and batch records. Significant body of

information available:

One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of information not available:

Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

b. Dissolution Documentation

Case B dissolution profile as described in Section III.B.2.b.

c. In Vivo Bioequivalence Documentation

Full bioequivalence study. The bioequivalence study may be waived with an acceptable in vivo/in vitro correlation has been verified.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

**SITE CHANGES**

Site changes consist of changes in location of the site of manufacture for both company-owned and contract manufacturing facilities and do not include any scaleup changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. Scale-up is addressed in Section V of this guidance. New manufacturing locations should have a satisfactory current Good Manufacturing Practice (CGMP) inspection.

A. Level 1 Changes

1. Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g.,temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.

2. Test Documentation

a. Chemistry Documentation

None beyond application/compendial release requirements.

b. Dissolution Documentation

None beyond application/compendial release requirements.

c. In Vivo Bioequivalence Documentation-None.

3. Filing Documentation-Annual report.

B. Level 2 Changes

1. Definition of Level

Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOP's, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry Documentation

Location of new site and updated batch records. None beyond application/compendial release requirements. One batch on long-term stability data reported in annual report.

b. Dissolution Documentation

None beyond application/compendial release requirements.

c. In Vivo Bioequivalence Documentation-None.

3. Filing Documentation

Changes being effected supplement; annual report (longterm stability test data).

C. Level 3 Changes

1. Definition of Level

Level 3 changes consist of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, the same equipment, SOP's, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the manufacturing batch records except for administrative information, location and language translation, where needed.

2. Test Documentation

a. Chemistry Documentation

Location of new site and updated batch records. Application/compendial releaserequirements.

**Stability:**

Significant body of data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long- term stability data reported in annual report.

b. Dissolution Documentation

Case B: Multi-point dissolution profile should be performed in the application/compendia medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.

c. In Vivo Bioequivalence Documentation-None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability data).

**CHANGES IN BATCH SIZE (SCALE-UP/SCALE-DOWN)**

Postapproval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production batches call for submission of additional information in the application. Scale-down below 100,000 dosage units is not covered by this guidance. All scale-up changes should be properly validated and, where needed,inspected by appropriate agency personnel.

A. Level 1 Changes

1. Definition of Level

Change in batch size, up to and including a factor of 10 times the size of thepilot/biobatch, where:

1) The equipment used to produce the test batch(es) is of the same design andoperating principles;

2) The batch(es) is (are) manufactured in full compliance with CGMP's; and

2. The same standard operating procedures (SOP's) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).Test

Documentation

Chemistry Documentation

Application/compendial release requirements. Notification of change and submission of updated batch records in annual report. One batch on long-term stability reported in annual report.

Dissolution Documentation None beyond application/compendial release requirements.

In Vivo Bioequivalence-None.

Filing Documentation-Annual report (long-term stability data).

Level 2 Changes

Definition of Level

Changes in batch size beyond a factor of ten times the size of the pilot/biobatch,

where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with CGMP'S; and 3) the same SOP's and controls as well as the same formulation and manufacturing procedures are used on the test batch(es) and on the full-scale production batch(es).

Test Documentation

Chemistry Documentation

Application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: One batch with three months accelerated stability data and one batch on long-term stability.

b.Dissolution Documentation-Case B testing.

c. In Vivo Bioequivalence-None.

3.Filing Documentation

Changes being effected supplement; annual report (long-term stability data).MANUFACTURING

Manufacturing changes may affect both equipment used in the manufacturingprocess and the

process itself.

A. Equipment

1.Level 1 Changes

a. Definition of Change

This category consists of:

1) Change from non-automated or non-mechanical equipment to automated ormechanical equipment to move ingredients; and

2) Change to alternative equipment of the same design and operating principles ofthe same or of a different capacity.

b.Test Documentation

i. Chemistry Documentation

Application/compendial release requirements.Notification of change and submission of updated batch records. Stability testing: One batch on long-term stability.

ii. Dissolution Documentation

None beyond application/compendial release requirements.

iii. In Vivo Bioequivalence Documentation-None

c. Filing Documentation-Annual report (long-term stability data).

2.Level 2 Changes

a. Definition of Level

Change in equipment to a different design and different operating principles.

Test Documentation

Chemistry Documentation

Application/compendial release requirements. Notification of change and submission of updated batch records.

Stability testing: Significant body of data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches

with three months accelerated stability data reported in supplement; up to three batcheson long-term stability

data reported in annual report.

Dissolution Documentation-Case C dissolution profile.

. In Vivo Bioequivalence Documentation-None.

Filing Documentation

Prior approval supplement with justification for change;annual report (long-

term stability data).

. Process

Level 1 Changes

Definition of Level

This category includes process changes including changes such as mixing times andoperating speeds

within application/validation ranges.

Test Documentation

Chemistry Documentation

None beyond application/compendial release requirements.

Dissolution Documentation

None beyond application/compendial release requirements.

. In Vivo Bioequivalence Documentation-None.

Filing Documentation-Annual report.

Level 2 Changes

Definition of Level

This category includes process changes including changes such as mixing times and

operating speeds outside of application/validation ranges.

Test Documentation

Chemistry Documentation

Application/compendial release requirements. Notification of change and submissionof updated batch records.

Stability testing: One batch on long-term stability.

Dissolution Documentation-Case B dissolution profile.

In Vivo Bioequivalence Documentation-None.

Filing Documentation

Changes being effected supplement; annual report (longterm stability data).

Level 3 Changes

Definition of Level This category includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.

Test Documentation

Chemistry Documentation

Application/compendial release requirements. Notification of change and submissionof updated batch records.

Stability testing:

Significant body of data available:

One batch with three months accelerated stability data reported in supplement; onebatch on long-term stability data reported in annual report.

Significant body of data not available:

Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

Dissolution Documentation-Case B dissolution.

. In Vivo Bioequivalence Documentation

In vivo bioequivalence study. The bioequivalence study may be waived if a suitablein vivo/in vitro correlation has been verified.

Filing Documentation

Prior approval supplement with justification; annual report (long-term stability data).IN VITRO DISSOLUTION

See current United States Pharmacopeia/National Formulary, section <711>, for general dissolution specifications. All profiles should be conducted on at least 12individual dosage units.

Dissolution profiles may be compared using the following equation that defines asimilarity factor where Rt and Tt are the percent dissolved at each time point. An f2 value between 50 and 100 suggests the two dissolution profil es are similar.

IN VIVO BIOEQUIVALENCE STUDIES

Below is a general outline of an in vivo bioequivalence study. It is intended as aguide and the design of the actual study may vary depending on the drug and dosage form.

. Objective:

To compare the rate and extent of absorption of the drug product for which the manufacture has been changed, as defined in this guidance, to the drug product manufactured prior to the change.

. Design:

The study design should be a single dose, two-treatment, two-period crossover with adequate washout

period between the two phases of the study. Equal numbers of subjects should be randomly assigned to each of the two dosing sequences.

. Selection of Subjects:

The number of subjects enrolled in the bioequivalence study should be determined statistically to account for the intrasubject variability and to meet the current bioequivalence interval.

. Procedure:

Each subject should receive the following two treatments:

Treatment 1: Product manufactured with the proposed change. Treatment 2: Product

manufactured prior to the proposed change.

Following an overnight fast of at least 10 hours, subjects should receive either Treatments 1 or 2 above with 240 mL water. Food should not be allowed until 4 hours after dosing. Water may be allowed after the first hour. Subjects should be served standardized meals beginning at 4 hours during the study.

. Restrictions:

Prior to and during each study phase, water may be allowed ad libitum except for 1 hour before and after drug administration. The subject should be served standardized meals and beverages at specified times. No alcohol or xanthine- or caffeine-containing foods and beverages should be consumed for 48 hours prior to each study period and until after the last blood sample is collected.

Blood Sampling:

Blood samples should be collected in sufficient volume for analysis of parent drug and active metabolite(s), if any. The sampling times should be such that it should be able to capture the Cmax and Tmax during the absorption period. Sampling should be carried out for at least three terminal elimination half-lives for both parent drug and active metabolite(s). Whole blood, plasma or serum, whichever is appropriate for the analytes, should be harvested promptly and samples should be frozen at -20oC or -70oC to maintain sample stability.

. Analytical Method:

The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method.

Pharmacokinetic Analysis:

From the plasma drug concentration-time data, AUC0-t, AUC0-inf, Cmax, Tmax, Kel and t1/2 should be estimated.

Statistical Analysis:

Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear models procedures of SAS or an equivalent program should be performed, with examination of period, sequence and treatment effects. The 90% confidence intervals for the estimates of the difference between thetest and reference least squares means for the pharmacokinetic parameters (AUC0- t, AUC0-inf, Cmax) should be calculated, using the two one-sided t-test procedure.

**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.

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 thePublic Health Service (PHS) Act.

The NDA review includes:

Medical Review(s) Chemistry Review(s)

Environmental AssessmentPharmacology

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 thefollowing key decisions

Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks

Whether the drug's proposed labeling (package insert) is appropriate and what itshould contain

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 mustcomplete a five-step process:

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

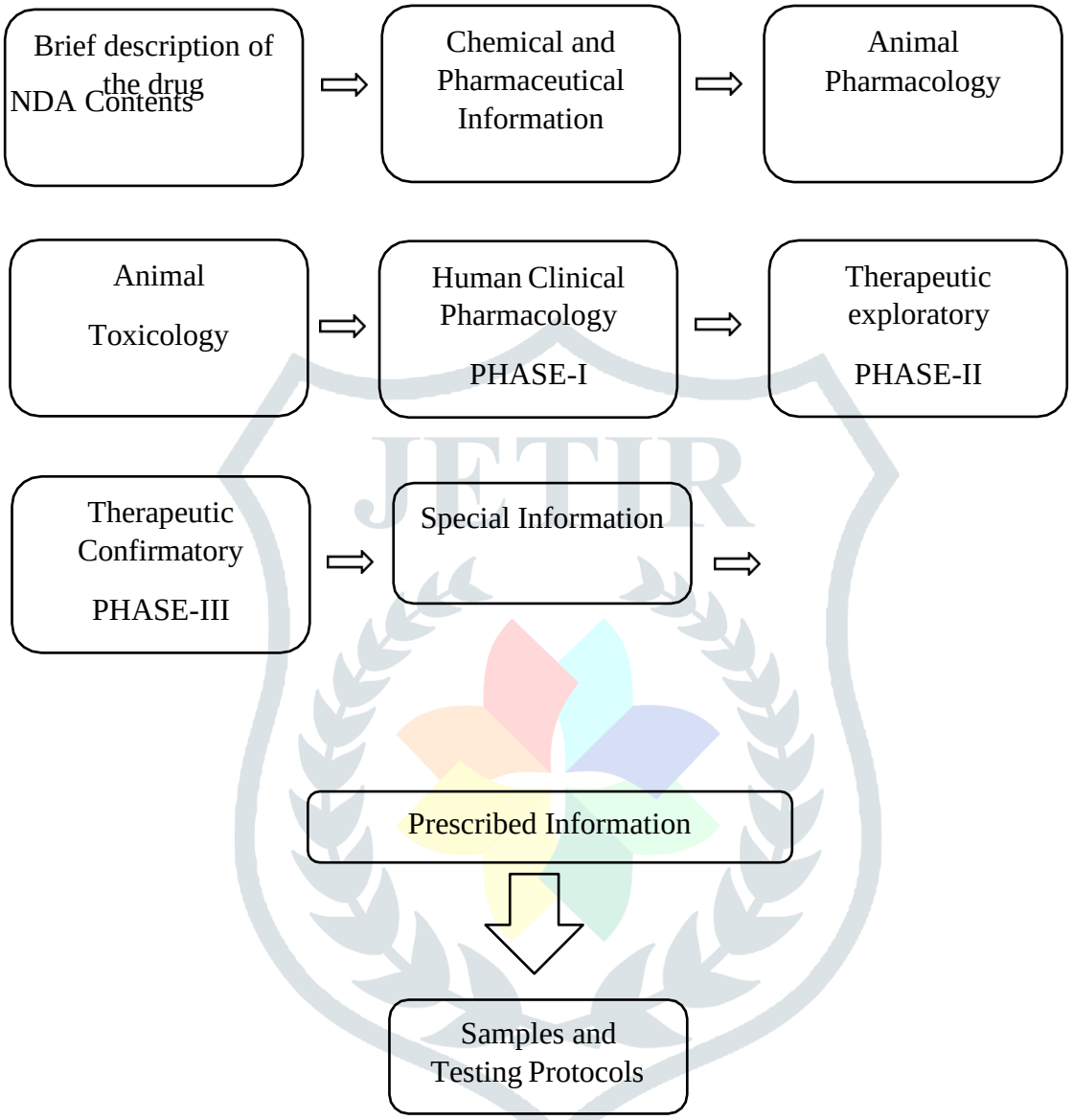
The aims of New Drug Application (NDA) include providing adequate information topermit FDA reviewers to establish the following:

Safety and effectiveness of drug,Benefits overweigh

risks,

Is the drug’s proposed labeling (package insert) appropriate, and what should it contain?

Are the methods used in manufacturing (Good Manufacturing Practice, GMP) the drug and the controls used to maintain the drug’s quality adequate to preserve the drug’s identity, strength, quality, and purity? Risk-Benefit.


Brief description of the drug
NDA Contents
Chemical and Pharmaceutical Information
Animal Pharmacology
Animal
Toxicology
Human Clinical Pharmacology
PHASE-I
Therapeutic exploratory
PHASE-II
Therapeutic Confirmatory
PHASE-III
Special Information
Prescribed Information
Samples and Testing Protocols

**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 thana 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.

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 asdirected

Reports on the design, compliance, and conclusions of completed clinicaltrials 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 therequirements of the applicable statutes and regulations.

If you want to discuss an alternative approach, contact the FDA staff responsible forimplementing this guidance.

## 1. Components and Composition

1.1. Any change made to comply with the official compendium, except relaxation of an acceptance criterion or deletion of a test (see 21 CFR 314.70(c)(2)(iii)).

1.2. Complete or partial deletion of an ingredient intended to affect only the color, flavor, or fragrance of the drug product without change in other approved specification. Note that a deletion or change in color, flavor, or fragrance also may affect the appearance and other noticeable organoleptic properties (visual appearance, taste, flavor, odor, or fragrance) of the dosage form. These changes may affect the "How the Drug Product is Supplied" section of labeling. In such cases, reporting of revision or change as described in Appendix A, 6. Labeling Changes, also would apply.

1.3. Change in non release controlling excipients, expressed as percentage (w/w) of total formulation approved in the original application, less than or equal to the following percent ranges: Filler ± 5%, Disintegrant (Starch ±3%, Other ± 1%), Binder ±0.5%, Lubricant (Calcium or Magnesium Stearate ±0.25%, Other ± 1%), Glidant (Talc ±1%, Other ±0.1%), and Film Coat ±1%.

1.4. Change in the supplier of an excipient, where the technical grade and specification for the excipient remain the same.

1.5. Changes in release controlling excipients less than or equal to 5% expressed as a percentage (w/w) of total release controlling excipients approved in the original application of a modified-release solid oral dosage form. After the change, the total weight of the dosage form and its specification would remain the same as originally approved.

**Manufacturing Site**

1. When the new site has a satisfactory CGMP inspection status for the type of operation14 involved, the following changes can be documented in an annual report:

1.1. A move to a different manufacturing site for secondary packaging, labeling, ink imprinting on a solid oral dosage form, and manufacture or processing of drug substance intermediates other than the final intermediate.

**Manufacturing Process**

1. For drug products, change to equipment of the same design and operating principles, capacity, and/or batch size (increase or decrease), except for natural protein drug substances and natural protein drug products.

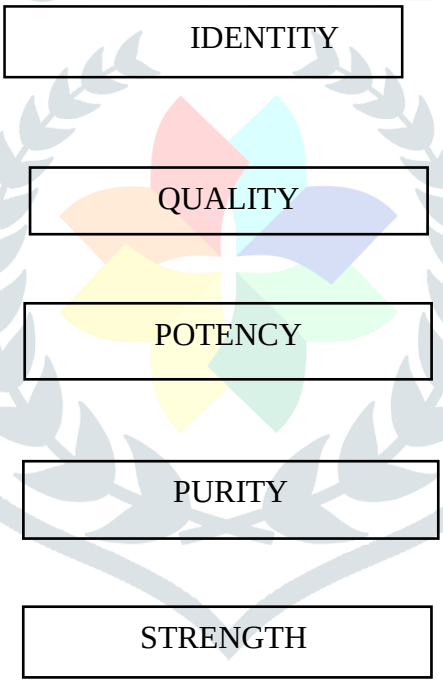
2. Change in the order of addition of drug product components for solution dosage forms (except active

pharmaceutical ingredients) or change in the order of ingredients added to solutions used in unit operations (e.g., granulation solutions).

**Specifications**

1. 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.

2. 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 final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the of the material being tested as the analytical procedure




**REPORTING CATEGORIES**

Section 506A of the Act and § 314.70 provide for four reporting categories that are distinguished in the following paragraphs.

**MAJOR CHANGE**: 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)).5

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 couldnot plan.

**MODERATE CHANGES:** 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)).

**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. 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 specifiedchanges.

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.

**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 CFRparts 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.

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)6 (§ 314.70(a)(5)).

## ASSESSING THE EFFECT OF MANUFACTURING CHANGES

### . 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)).7 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 thechange conform to the approved specifications.

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.

. Equivalence

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.

. 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 changes-being-effected-in-30• days supplement could cause the formation of a new degradant that requires qualification and/or identification. 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.

**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 includethose used by an applicant to

(1) Manufacture or process drug products,12 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 inthe 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 inspection13 for the type of operation14 being moved.

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 reportedto 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.

Examples for 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 approvalsupplement (see sections VI.B.1 and 2).

A move to a different manufacturing site for secondary packaging.

A move to a different manufacturing site for labeling.

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

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

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

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

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.

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).

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

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.

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.

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

**SPECIFICATIONS**

. 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 proceduresfor 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 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.

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)).

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.

Tightening of acceptance criteria.

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 final intermediate, 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.

**CONTAINER CLOSURE SYSTEM**

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 theapproved 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.

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.

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.

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)).

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

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.

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:

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

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 a metal to plastic screw cap, or changing from a plastic to metal screw 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 (e.g., heat induction seal).

A change in the container closure system of unit dose packaging (e.g., blister 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).

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 usedin 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.

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.

**LABELING**

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.

**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 reportingcategory.

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.

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

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

Labeling changes made to comply with an official compendium

**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.

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)).

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

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

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.

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

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

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 providegreater assurance of drug product purity and potency.

**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.

**Domestic Establishments**

Same manufacturing site:

The new and old buildings are included under the same drug establishmentregistration number25 and

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

Different manufacturing site:

The new and old buildings have different drug establishment registrationnumber

or

Different FDA district offices are responsible for inspecting operations in thenew and old buildings.

For domestic establishments, the terms same manufacturing site and different manufacturing site supersede the terms contiguous campus, same campus, and differentcampus 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 anddifferent 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 cityblocks.

**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 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).

Certain inspections may be required by program priorities even if the rating for a profile class code indicates an acceptable CGMP status.

CGMP inspectional status, based on the profile class, is available through FDA's Freedom of Information (FOI) Office. (See Glossary under Satisfactory Current Good Manufacturing Practice (CGMP) Inspection for more information regarding FOI requests.) 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 operationsincluded 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 thatparticular 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.

**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 substancespecific 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 section VI.C.1.d.

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-approveddrug 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.

**GENERAL STABILITY CONSIDERATIONS**

The effect SUPAC-type changes have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, applicants are referred to the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics (02/87).

For SUPAC submissions, the following points also should be considered:

In most cases (except those involving scale up), stability data from pilot scale batches will be acceptable to support the proposed change. Where stability data show a trend toward potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative

prechange batch be submitted for comparison. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement. Submission of historical accelerated and available long- term data would facilitate review and approval of the supplement.

A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on the first or first three (see text for details) production batches and to report the results in the annual reports.

**COMPONENTS AND COMPOSITION — NONRELEASE CONTROLLINGEXCIPIENT**

This section of the guidance focuses on changes in nonrelease controlling excipients in the drug product. For modified release solid oral dosage forms, consideration should be given as to whether the excipient is critical or not critical to drug release.

The sponsor should provide appropriate justifications for claiming any excipient(s) as a nonrelease controlling excipient in the formulation of the modified release solid oral dosage form. The functionality of each excipient should be identified. Changes in the amount of the drug substance are not addressed by this guidance.

Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at level 3 (defined below), except as described below in Section III.A.1.a. Waiver of bioequivalence testing for a change in composition which involves only a different color, flavor or preservative may bepermissible as described in 21 CFR 320.22(d)(4).

Level 1 Change

Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact onformulation quality and performance.

Examples:

Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.

Changes in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:

Nonrelease Percent Excipient (w/w) Out of Controlling Total Target Dosage FormExcipient Weight

| |
|---|
| Filler ±5 |
| Disintegrant |
| Starch ±3 |
| Other ±1 |
| Binder ±0.5 |
| Lubricant |
| Ca or Mg Stearate ±0.25 |
| Other ±1 |
| Glidant |

| |
|---|
| Talc ±1 |
| Other ±0.1 |
| Film Coat ±1 |

These percentages are based on the assumption that the drug substance in the product is formulated to 100% of label/potency. The total additive effect of all

Example: In a product consisting of active ingredient A, lactose, microcrystalline cellulose, and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5% (e.g., lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%) relative to the target dosage form weight if it is to stay within the level 1 range. nonrelease controlling excipient changes should not be more than 5%.2 The total weight of the dosage form should still be within the original approved application range.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the original approved target composition and not on previous level 1 changes in the composition. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

Test Documentation

a. Chemistry documentation Application/compendial product

release requirements.

Stability: First production batch on long-term stability data reported in annual report.

Dissolution documentation

None beyond application/compendial requirements.

Bioequivalence documentation

**COMPONENTS AND COMPOSITION — RELEASE CONTROLLING EXCIPIENT**

This section of the guidance focuses on changes in release controlling excipients in the drug product. For modified release solid oral dosage forms, consideration should be given as to whether or not the excipient is critical to drug release. The sponsor should provide appropriate justifications (i.e., mechanism of drug release and manufacturing process) for claiming any excipient(s) as a release controlling excipient in the formulation of the modified release solid oral.

Example: In a product consisting of active ingredient A, ethylcellulose and a plasticizer, the ethylcellulose and plasticizer content should not vary by more than an absolute total of 5% w/w of the total release controlling excipients (e.g., ethylcellulose content increases by 2.5% and plasticizer content increases by 2.5%) relative to the original approved total release controlling excipient content weight in the modified release solid oral dosage form if it is to stay within the given range allowed for level 1. dosage form. The functionality of each excipient should be identified. Changes in the amount of the drug substance are not addressed by this guidance. Changes exceeding the ranges defined in each of the levels below may be allowed if considered to be within normal batch-to-batch variation and contained within an approved original application. In such situations, sponsors should contact the appropriate CDER review division for further guidance.

. Level 1 Change

Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

**Example:**

Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation less than or equal to 5% w/w of total release controlling excipient content in the modified release solid oral dosage form. The drug substance in the product is formulated to 100% of

label/potency. The total additive effect of all release controlling excipient changes should not be more than 5% w/w of the total release controlling excipients in the original approved formulation.4 The total weight of the dosage form should still be within the approved original application range.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the original approved target composition and not on previous level 1 changes in the composition. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range Test Documentation

a. Chemistry documentation Application/compendial product

release requirements.

Stability: First production batch on long-term stability data reported in annual report.

Dissolution documentation

None beyond application/compendial requirements.

c. Bioequivalence documentationNone.

3. Filing Documentation

Annual report (all information including long-term stability data).

**SITE CHANGES**

Site changes consist of changes in location of the site of manufacture, packaging operations, and/or analytical testing laboratory for both company-owned and contract manufacturing facilities.

They do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. New manufacturing locations should have had a satisfactory current good manufacturing practice (cGMP) inspection.

A stand-alone packaging operations site change, using container(s)/closure(s) in the approved application, may be submitted as a Changes Being Effected supplement. The facility should also have a current and satisfactory cGMP compliance profile with the FDA for the type of packaging operation in question before submitting the supplement.

If the facility has not received a satisfactory cGMP inspection for the type of packaging operation in question, a prior approval supplement is recommended. The supplement should contain a written certification from the packaging facility stating that it is in conformance with cGMPs. It should also contain a commitment to place the first production batch of the product, and annual batches thereafter, on long-term stability studies using the approved protocol in the application and to submit the resulting data in annual reports.

Where the product is available in more than one strength, size, or container/closure system, one lot of each combination should be placed on long-term stability studies.

Bracketing or matrixing is allowed only if it has been approved previously by theFDA.

Any changes to an approved stability protocol should have a supplemental approval prior to the initiation of the stability study.

Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.

A stand-alone analytical testing laboratory site change may be submitted as a Changes Being Effected supplement if the new facility has a current and satisfactory cGMP compliance profile with the FDA for the type of testing operation in question.

The supplement should contain a commitment to use the same test methods employed in the approved application, written certification from the testing laboratory stating that they are in conformance with cGMPs, and a full description of the testing to beperformed by the testing lab.

If the facility has not received a satisfactory cGMP inspection for the type of testing involved, a prior approval supplement is recommended.

Level 1 Change

Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOPs), environmental conditions (e.g., temperature and humidity) and controls, and personnel common7 to both manufacturing sites are used and where no changes are made to the executed batch records, except for administrative information and the location of the facility.

Test Documentation

Chemistry documentation

None beyond application/compendial product release requirements.

Dissolution documentation

None beyond application/compendial release requirements.

Bioequivalence documentation
None.

3. Filing DocumentationAnnual report.

**CHANGES IN BATCH SIZE (SCALE-UP/SCALE-DOWN)**

Postapproval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production batches call for submission of additional information to the application.

Scale-down below 100,000 dosage units is not covered by this guidance. Adjustments in parameters such as mixing times and speeds may be made to tailor the process to the characteristics of larger or smaller scale equipment. All scale-up changes should be properly validated and, where needed, inspected by appropriate Agency personnel.

. Level 1 Change

Definition of Level

Change in batch size, up to and including a factor of ten times the size of the pilot/biobatch, where (1) the equipment used to produce the test batch(es) may vary in capacity, but are of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

Test Documentation

Chemistry documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records in annual report. Stability: First production batch on long-term stability data reported in annual report.

**MANUFACTURING EQUIPMENT CHANGES**

Manufacturing changes may involve the equipment used in the manufacturing process (critical manufacturing variable). If a manufacturer wishes to use manufacturing equipment that is not identical in every respect to the original manufacturing equipment used in the approved application, appropriate validation studies should be conducted to demonstrate that the new equipment is similar to the original equipment. For modified release solid oral dosage forms, consideration should be given as to whether or not the change in manufacturing equipment is critical to drug release (critical equipment variable).

. Level 1 Change

Definition of Level

This category consists of (1) change from nonautomated or nonmechanical equipment to automated or mechanical equipment to move ingredients and (2) change to alternative equipment of the same design and operating principles of the same or of a different capacity.

Test documentation

Chemistry documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability: First production batch on long-term stability data reported in annual report.

Dissolution documentation

None beyond application/compendial release requirements.

c. Bioequivalence documentationNone.

Filing Documentation

Annual report (all information including long-term stability data).

**MANUFACTURING PROCESS CHANGES**

Manufacturing changes may involve the manufacturing process itself (critical manufacturing variable). If a manufacturer wishes to use a manufacturing process that is not identical in every respect to the original manufacturing process used in the approved application, appropriate validation studies should be conducted to demonstrate that the new process is similar to the original process. For modified release solid oral dosage forms, consideration should be given as to whether or not the change in manufacturing process is critical to drug release (critical processing variable). For purposes of categorizing the level of changes, process change may be considered only to affect a release controlling excipient when both types of excipients (i.e., nonrelease and release controlling) are present during the unit operation undergoing a change.

Definition of Level

Process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds within original approved application ranges affecting the nonrelease controlling and/or release controlling excipient(s). The sponsor should provide appropriate justifications for claiming any excipient(s) as a nonrelease controlling or a release controlling excipient in the formulation of the modified release solid oral dosage form.

Test Documentation

Chemistry documentation

None beyond application/compendial product release requirements. Notification of the change and submission of the updated executed batch records.

Dissolution documentation

None beyond application/compendial release requirements.

c. Bioequivalence documentationNone.

3. Filing DocumentationAnnual report.

## CONCLUSION

This thesis describes chemistry, manufacturing, and controls (CMC) postapproval manufacturing changes that FDA generally considers to have a minimal potential to have an adverse effect on product quality. Under FDA regulations, postapproval changes in the product, production process, quality controls, equipment, facilities, or responsible personnel that have a minimal potential to have an adverse effect on product quality must be documented by applicants in an annual report. This guidance applies to biological products, as defined in 21 CFR 600.3(h), that fall under one of the following categories specified in 21 CFR 601.2(a): therapeutic DNA plasmid products, therapeutic synthetic peptide products of 40 or fewer amino acids, monoclonal antibody products for in vivo use, and therapeutic recombinant DNA-derived products.4 It also applies to combination products licensed under a BLA, where the biological product constituent part falls under one of these categories specified in 21 CFR 601.2(a). The guidance does not apply to blood or blood components, blood-derived products, in vitro diagnostics, cellular and gene therapy products, or vaccines and related products5 ; however, a BLA holder for any other naturally derived biological product should discuss with FDA whether the recommendations in this guidance apply to his or her BLA.

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