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Regulatory requirement for Pre & Post-approval management of Generic Drugs in US

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Abstract

FDA is a federal agency within the Department of Health and Human Services & important regulated body. In accordance with FDA regulations under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) this review explains how to file an abbreviated new drug application (ANDA). The data in an ANDA Submission to FDA, CDER, Office of Generic Drugs, allows for the evaluation and potential authorization for a generic drug product. After receiving approval, an application is allowed to manufacture and market the generic drug product so that the general public has access to a secure, efficient, and affordable substitute.

A generic medicine is a therapeutically equivalent, safe, and more affordable substitute for the market-leading innovator or branded drug. The US has one of the most stringent regulatory authorities. The application to be submitted for registering generic drugs is known as an ANDA. Making sure that medication development, manufacture, and testing have been done in accordance with the rules and norms and that everything has been properly documented is one of the regulatory authorities' key responsibilities. The International Conference on Harmonization (ICH) created a standardized application format for registering medicinal products. In order to obtain market authorization in the US, this paper addresses the generic medication registration requirements in the form of an eCTD dossier.

The term "post approval changes" refers to modifications made to the approved generic and marketed drug products. These modifications are made in order to provide the data necessary to assess whether the proposed changes will have an adverse effect on the quality of the approved products in terms of their safety, efficacy, and effectiveness. The applicant may make post-approval amendments after the NDA or ANDA has been approved, provided that the changes are disclosed to the FDA in accordance with the necessary categories. Company change control processes should include information on how changes are assessed, implemented, and effect on product stability along with appropriate data and justification required justifying the proposed change. Based on an examination of the technical evaluation of the change and the pertinent regulatory guidelines, the regulatory group will determine the submission method.

Keywords: Orange Book, CDER, ANDA, NDA, FDA, Paragraph IV certifications, RTR, Generic drugs, Common technical document, USFDA, Hatch Waxman act, Post-Approval Changes, SUPAC guidelines.

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1. Introduction

1.1 The United States food and drug administration (USFDA) (1-3)

The Food and Drug Administration of the United States (FDA or USFDA) is a federal agency within the Department of Health and Human Services. The FDA regulates and oversees a variety of industries, including food safety, tobacco products, dietary supplements, prescription and over-the-counter medications, vaccines, biopharmaceuticals, blood transfusions, medical devices, equipment that generate electromagnetic radiation (ERED), cosmetics, animal feed and food, and veterinary items.

Regulation of Food, Drugs, and Cosmetics (FD&C) is the FDA's main domain of enforcement, although it also carries out other legal obligations, such as Section 361 of the Act on the Public Health Service. In

addition to regulating condoms, lasers, and cell phones, this regulatory work also focuses on disease prevention in a variety of situations, from domestic pets to human sperm donated for assisted conception.

1.2 Introduction to abbreviated new drug application (4)

A generic drug product's data is included in an abbreviated new drug application (ANDA), which is submitted to the FDA for evaluation and approval and the ANDA application holder can market the generic drug product after it has been approved in order to provide a reliable, cost-effective substitute for the reference listed product to which it corresponds.

Preclinical and clinical evidence to show safety and effectiveness are typically not necessary for ANDA application. The ANDA applications for generic drugs are sometimes referred to as" abbreviated new drug application". Instead, applicants for generic drugs must use science to show that their product works similarly to the drug innovator. Bioequivalence studies to be perform on the generic drug product to prove that it functions similarly to the innovator drug. (5)

This "bioequivalence" demonstration provides the generic medicine's bioavailability or absorption rate which may compared with that of the innovative drug that is awaiting FDA approval. The generic version of the innovator drug must release the same amount of active ingredients into the patient's bloodstream over the same period of time.

However, the agency provides patents to the RLD for a limited time in order to keep medication inexpensive and cost-effective then arrive and play the generic players. The manufacturers of generic medications must demonstrate that their products meet all of the agency's requirements for labelling and other things, including that their generics are safe and bioequivalent to approved RLDs.

ANDA Filling is most important for the generic drugs companies for marketing with low cost compared to branded drug. A Drug is filed through Abbreviated New Drug application (ANDA Pathway) when the generic version is:

- Pharmaceutical equivalents
- Therapeutic Equivalents
- Bio-equivalency to RLD

1.3 Pharmaceutical equivalents (6-8):

When a drug product is identical to a reference listed drug (RLD) in terms of dosage forms and route(s) of administration and contains the same amount of the same active drug ingredient, i.e., the same therapeutic moiety as well as the same identity, strength, quality, and purity, including potency and, where requirement applicable to the Agency, then the drug product is said to be pharmaceutical equivalents.

1.4 Therapeutic Equivalents:

Therapeutic equivalents are defined as When given to patients according to the instructions on the label, licensed medication products that are pharmacological counterparts for which bioequivalence has been established are expected to have the same clinical effect and safety profile.

1.5 Bio-equivalency to RLD:

The generic drugs manufacturer must prove that their product is bioequivalent to a brand-name or reference-listed drug in order for an ANDA to be granted.

1.6 Bioequivalence (BE):

There isn't a noticeable difference between how quickly and how much the drug is made available at the site of action. Same clinical effect and safety profile under the conditions specified in the labelling**.**

2. Generic drug product registration requirements in the USA (8-9):

a) For the submission of drug applications (NDA/ANDA), the eCTD is required.

b) To prepare the dossier for drug approval applications, US FDA guidelines (21CFR) guidelines and FDA sections (such as 505(b) for NDA and 505(j) for ANDA) are observed.

c) The Applications come in several forms:

- NDA stands for new drug applications
- ANDA for generic drugs,
- BLA for biological applications.

d) The FDA may receive the application directly from the applicant or from a Generic Drug Enforcement Act and licensed agent which is based in US.

e) Cover letters, applications (356h), information about the application, field copy certification, debarment certification, and financial certification, Patent information, and exclusivity are not the same as administrative information.

f) Letter size (8.5x11 inches) paper in Times New Roman style with a font size of 12 is required for submission. The font size for the tables and figures ranges from 8 to 10 may be acceptable.

g) Package inserts are provided for drug product in labelling.

h) Generic labels with proposed RLD (Reference Listed Drugs) labels and boxes with correct dimensions are presented.

i) The financial disclosure Statement component of this module and Module 5 both contain information about the clinical investigators.

j) Module 1 contains a request for a waiver of in-vivo BE tests.

k) Annotated draft Labelling is provided with the appropriate annotation for labels and cartons

compared to the RLD. Labelling is provided with the appropriate annotation for labels and cartons compared to the RLD.

l) According to US law's EPA Environmental Assessment Statement (EAS) for categorical exclusion under (Environmental Protection Act) certification is provided.

m) The risk management plans part addresses post-marketing monitoring and effective treatment of pharmacological side effects. This is the fourth phase of the clinical trial.

n) According to USP, a declaration is made regarding the maximum amounts of residual solvents utilized is included in the drug's active ingredient and excipients.

o) The 3.2.R format contains information about components, such as the supplier or manufacturer's name and address for raw materials, packaging materials, etc.

p) Certificate of suitability (CEP certificate) is not applicable.

q) There are no protocols for comparability related to the drug substance or the drug products.

r) The USFDA requires study tagging files (STF) and structured product labelling (SPL) in the electronic submission of a drug registration application (eCTD).

2.1 Regulation review process under ANDA (10-11):

When an applicant files from ANDA to CDER (Centre for Drug Evaluation and Research), the ANDA procedure gets started. The ANDA is processed by the document room employees, who additionally assign an ANDA number, stamp a date of receipt on a cover letter. Technician for consumer protection next receives the ANDA and goes for review as per the ANDA checklist. The filed ANDA is examined while taking the drug's bioequivalence, chemistry, microbiology, and labelling into account. A file review is finished during the initial approx. 60 days after an ANDA is submitted to provide acceptance to receive for review.

The accompanying Figure provides a flowchart of the simplified USFDA ANDA regulatory review procedure.

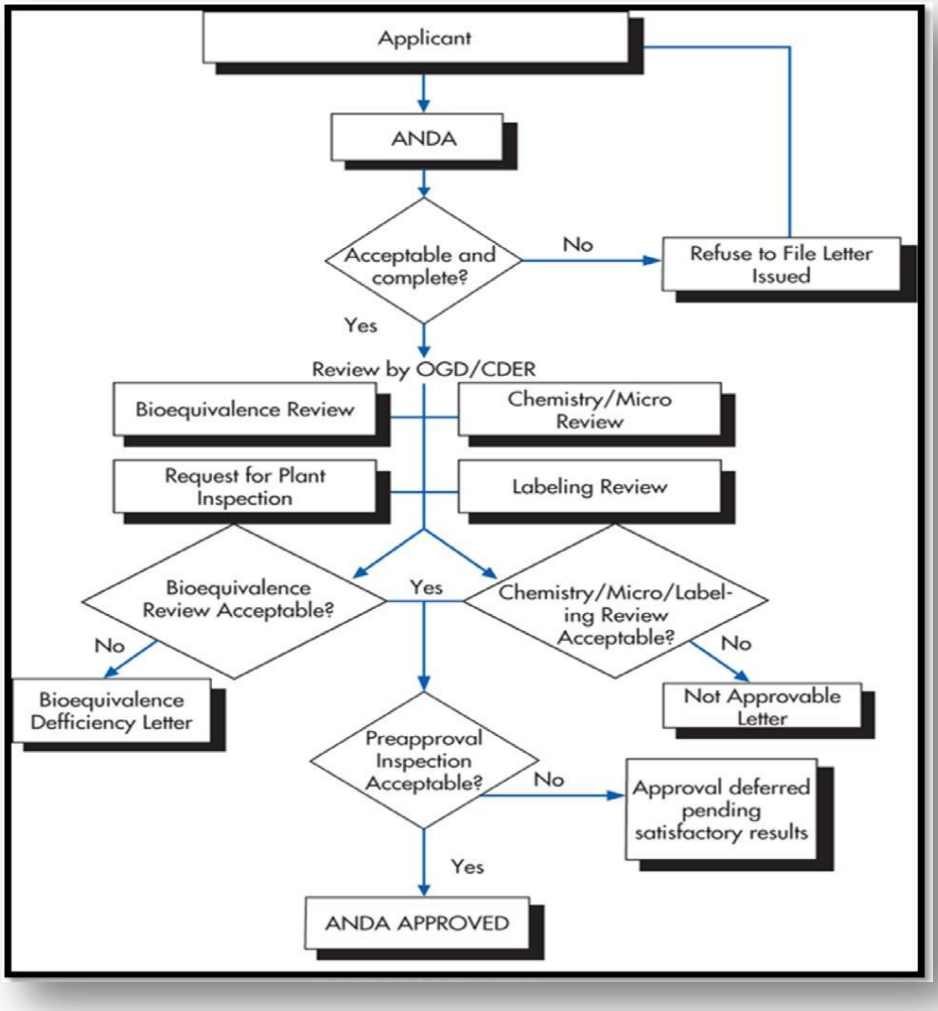

Figure 1. ANDA Review Process (11)

2.2 Bio Equivalence Review Procedure:

The two main conditions for a generic medicine to be therapeutically equivalent to the innovator drug are pharmaceutical and bioequivalence. Both the original drug and the generic must be equally potent, dosage form, and method of administration in order to be considered pharmaceutically similar. When the products are studied in the same manner and exhibit a comparable bioavailability, they are regarded as being bioequivalent to determine bioequivalence, the maximum drug concentration (C max) and the AUC are both used. A generic product is considered to be bioequivalent to the branded one if its relative mean C max and a 90% confidence interval (CI) of the mean the area under the curve are between 80% and 125% product.

2.3 Review Process for Labels

The purpose of the labelling review procedure is to make certain that the generic drug and the innovator drug have the same labelling. After the final administrative review and each discipline have made the necessary corrections, the application will either receive a letter of complete approval or a letter of provisional approval.

2.4 ANDA Approved

An acceptance or provisional approval letter is given to the applicant if all application components have been considered acceptable. A provisional authorization letter is given to the applicant if the approval takes place before any exclusive rights or patents related to the reference listed drug product have expired. This letter explains the circumstances surrounding the approval of the generic medicinal product is provisional and delays approval until all exclusivity or patent issues have been resolved.

2.5 Hatch Waxman act:

Hatch-Waxman Act (Act of 1984 (drug price competition and patent term restoration). The Act, which amended the Act on Food, Drugs, and Cosmetics created a "regulatory framework designed to balance incentives for continued innovation among research-based pharmaceutical companies with opportunities for market entry by generic drug manufacturers" by using the Abbreviated New Drug Application (ANDA) Process to request FDA permission for the generic drug's marketing prior to the branded product's patent expiration and to get the market exclusivity of 180 days.

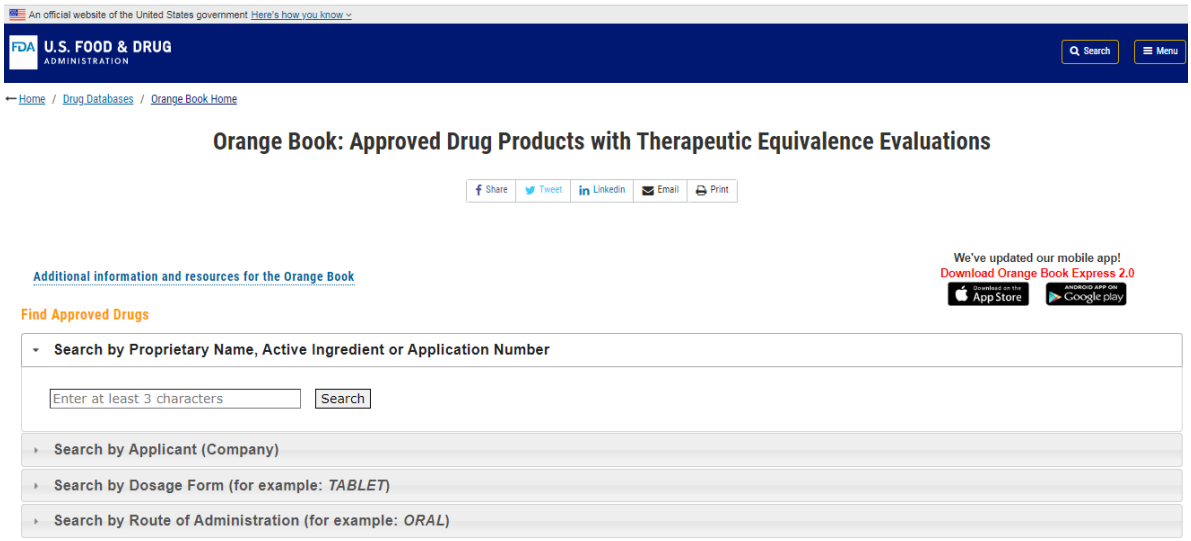

Figure 2. Orange book Listing (7,11)

An innovative drug product's dosage form, strength, administration method, performance, and quality traits, and intended usage are all examples of generic drug products. Orange Book is a list both innovator and generic products that have been approved.

Every generic drug that has been authorized by the FDA and is appearing in the Orange Book is kept in a database.

2.6 ANDA submission review process (12-13):

An organization doesn't need to do extensive clinical trials to receive approval for a generic medicine. To demonstrate that their generic drug is "equivalent" to the innovator drug that had previously received approval, the business instead conducts bioequivalence studies. The generic company may make references to certain sections of the NDA that the brand name company provides when it submits an ANDA.

ANDA only applies to generic version of NCE (New Chemical Entity). NCE means a drug that was not previously approved by FDA. It does not include biological products like proteins or antibodies. For a generic drug, an ANDA can be submitted 4 years after the corresponding NCE was approved, but ANDA itself cannot be approved until at least 5 years after NCE approval by FDA.

Applicant will select the generic product and innovator for ANDA submission along with certification clause. Submission requirement shall be followed as per requirement of respective clause selected for product.

The applicant must put together the dossier according to the below e-CTD modules while keeping in mind the ANDA format instructions:

2.7 Modules in CTD:

1. MODULE I: Administrative and Prescribing Information
2. MODULE II: Summaries and Overviews
3. MODULE III: Information on product quality
4. MODULE IV: Non-Clinical Study Reports (not required for ANDA filing)
5. MODULE V: Clinical study reports

After Fee payment as per GDUFA, Applicant shall apply complete set of dossiers required sections for ANDA Document Submission. Once applied by Applicant, Agency reviewer team will review as per their standard guidelines and norms.

Upon finding of discrepancies/queries, Agency will issue IR (information request), CR (complete response letter), DRL (Discipline review letter) based on criticality of observation and Applicant has to respond the same within stipulated timeline to have successful submission and approval.

If USFDA Agency detects any negative RTR observation, they would reject the application by issuing RTR letter and again Applicant has to file the ANDA to have successful submission and approval.

A company intending to market a generic version of a listed drug must certify one of the following four certifications regarding the patents listed in connection with the innovator's NDA.

The following includes other Post approval changes terms are as follows;

I. Complete Response Letter (CRL)

Complete Response letter is issued to the applicant, when the FDA determines that they will not approve the application in question in its present form due to any deficiencies, pending amendment review, if the submission contains inadequate data.

II. Discipline Review Letter (DRL)

Deficiency Review Letter is received from the agency containing initial review of the documents containing deficiencies. Applicant should respond to the deficiencies mentioned in the DRL within the mentioned time frame for timely completion of the review of the Submission.

III. Information Request

It is an FDA way of asking more information, documentation, clarification for completing the review. FDA through IR, generally asks information which are needed during the review of either of labelling, quality or bio-equivalence discipline.

The following are the selection criteria for application of product in respective Patent Certification clause:

2.8 Patent Certification clauses:

Paragraph I certification: No patent in New Drug Application: This certification is for a drug that is mentioned in "Orange Book" that does not include a patent as part of it of the NDA. Every ANDA that makes this certification must have FDA approval.

Paragraph II Certification: The NDA's patent(s) are no longer valid: An NDA with one or more expired patents is covered by the certification. Once more, FDA must approve any ANDA that makes this certification.

Paragraph III Certification: Patent(s) in the NDA are still in effect: This certification certifies that the generic producer will submit an ANDA for approval following the expiration of any relevant patent(s). The FDA can only approve an ANDA with a Paragraph III Certification after all patent(s) in NDA have expired.

Paragraph IV Certification: Patent in NDA is invalid or generic equivalent product does not infringe: By using this certification a generic manufacturer can either challenge the validity of applicable patents in NDA or certify that generic equivalent No patents owned by the original pharmaceutical business, whose patent(s), the product will not infringe the part of NDA.

The fourth certification, paragraph IV, is the most challenging. In accordance with this, the generic company must also inform the innovator company of the filing of the ANDA and provide justification for its opinion that the patent listed is not valid or the non-infringement of the generic version upon it. The innovator company has 45 days from notification to launch a lawsuit for infringement. The FDA will delay approving an ANDA for 30 months or until the case is resolved if such a lawsuit is filed. Future FDA actions will be determined by the case's outcome. ANDA is approved, for instance, if it is determined that the generic product complies with the confidential claims.

If ANDA is approved by FDA, then generic company obtained a period of 180 days during which it could exclude any other prospective generic market entrant from marketing the same generic product based upon same pioneer drug. Following the first sale of a generic drug by a manufacturer, the 180-day exclusivity period generic after receiving FDA has authorized its ANDA.

180-day Exclusivity for ANDA Application: The first ANDA filer who certifies Para IV and disputes the patent benefits. The first of these generic businesses allows for 180 days of exclusivity to the ANDA filler. For 180 days, the FDA will not permit the release of another generic.

30 Month Stay: The first ANDA applicant who files with Paragraph IV certification triggers a 30 month stay, during which ANDA application will not be approved by FDA unless there is a favourable court decision in the interim. The ANDA filing itself may be taken as an act of infringement. The NDA holder gets notice of ANDA application with Para IV

certification and a patent infringement lawsuit within 45 days lawsuit (14)

2.9 Types of Approval:

a.Tentative Approval

b.Final Approval

a). Tentative Approval:

It is not final approval for commercializing a drug product, The agency will issue when it completes the review of ANDA Application they conclude that the data contained in the application is correct.

Drug Products are given tentative approval when,

1.RLD upon which the ANDA application is based is on subjected to periods of patent protection.

2.Any other regulatory exclusivity related to drug product.

To request final approval for a tentatively approved product, application needs to submit an amendment designated FINAL APPROVAL REQUESTED in the cover Letter.

b). Final Approval:

Final approval is the approval granted by the agency which authorizes the generic makers for commercialization of the product. Full approval is granted after full assessment of the application by different office of the agency.

3. Introduction to post- approval management (15-16)**:**

Post approval management is the management of an already approved ANDA drug product. If there are no delays during the FDA's evaluation, the ANDA application for generic product approval that is submitted to the agency (US-FDA) is reviewed in about 10 months However, this ANDA must undergo post-approval monitoring up until the drug product is distributed commercially.

A post-approval change management describes exactly what changes the company would like to make during the product's lifecycle as well as how they would be prepared and established. Since the Marketing Authorization Holder will have secured approval from the Regulatory Authorities regarding the proposed strategy and tests to confirm the impact of the change on product quality, such a stepwise approach is anticipated to lead to faster and more predictable implementation of changes post-approval.

The objective of this study is to classify the changes made to generic and marketed drug products that have received an approval and to provide the data to support a change which would be considered sufficient to allow a determination of the impact of the Changes to the approved ANDA' quality in terms of their safety, effectiveness, and/or efficiency of use.

Notifications are submitted to an agency after the implementation of the change in the product to but the change should not possess major risk i.e., minor change in nature. However, supplements are exposed to an agency post approval to revise something which has been approved. This concept clearly gives traces to why major changes are named ‘‘Prior approval supplement’’.

In post approval management, the product's lifespan is maintained after receiving agency approval. For efficient medication lifecycle management, numerous queries, updates, compliance, & notification are added to the authorized application. These activities can range from any change in manufacturing process, vendor change, and change in labelling of RLD to submission of vigilance reports through submission of annual report. The documents are submitted in the agency required format i.e.-eCTD. Since the original submission is of sequence 0001, Also it is included in submission number.

3.1 Scale - up and post-approval changes (SUPAC) regulations *(17-18)**:***

The creation of a palatable version of the medicinal active component is the aim of product development. The term "scale-up" describes the technical transition of a pharmaceutical product from research to manufacturing (often referred to as the "shop floor") while also increasing production outputs. Expanding batch size is referred to as "scaling up" in technical language. Contrarily, scale-down describes a reduction in batch size in reaction to a decline in market demand. A lot of problems arise when shifting scales from the research lab to the factory floor. These problems are caused by the usage of numerous processing instruments both in research and on the shop floor. The complexity of a pharmaceutical process, which may involve a number of different unit operations, the lack of information about the equipment, various process control requirements, the complexity of the equipment, the behaviors of the ingredients at different scales, as well as trial-and-error methodology are all major contributors to scale-up problems. Every product created through research should be able to be produced, and the production method itself ideally be able to show its durability on the production line. This assertion highlights the significance of scaling up and transferring technologies in the process of developing pharmaceuticals.

Following the successful completion of technology transfer and validation processes, a product often operates without any problems on large-scale manufacturing equipment. A drug product's chemical and manufacturing procedure are altered after approval and remain altered for the duration of its use. Depending on anticipated (or unanticipated) requirements, changes in raw materials, procedures, equipment, manufacturing site, and batch size can all affect the quality attributes of a drug or final product. As a result, it's critical to anticipate and carefully evaluate how each adjustment will affect the final product's or medicine's quality. These modifications could be the result of a number of factors, such as a change in the production process, an improvement in the packing materials, a transfer to a new analytical

methodology, or a change in the raw material source. during all phases of its life, a medicine or drug product may undergo numerous alterations. These modifications may have a detrimental influence on the drug's or product's overall safety and effectiveness. The product that eventually makes it to market may be completely different from the one that was approved after a series of adjustments over a long period of time.

As a result, a comparison between the medicine or drug product and the one that was first approved must be included in the data provided to regulatory authorities in support of a change. The regulatory authority receives the supporting documentation for any modification to an approved drug or drug product for evaluation, and the medicine and/or medicinal product is approved based on the benefit-to-risk balance. Depending on the seriousness of the adjustment, supporting documentation are provided to the regulating agency. Pharmaceutical companies are required to adhere to scale-up and post-approval changes (SUPAC) guidelines by regulatory organization the United States FDA, the Food and Drug Administration and others in order to maintain the quality of the drugs produced. To keep up with technological advancements, the rules are regularly evaluated, and new recommendations are created to reduce the burden on the FDA regulations and the pharmaceutical sector organizations.

3.2 CMC sections of regulatory filings:

The chemistry, manufacturing, and controls (CMC) portion of a regulatory new drug application (NDA) or abbreviated new drug application, as well as post-approval CMC supplements, offers comprehensive details regarding the properties, manufacturing processes, and quality elements of the drug substance and drug product. The Common Technical Document (CTD) of the International Conference on Harmonization (ICH) format refers to the CMC section as the quality section, and the ICH CTD guidance describes the structure.

3.3 Post approval changes: USFDA (19-21)

The term "change's definition is "any modification to any aspect of a pharmaceutical product, including but not limited to formulation, technique, and packaging" the manufacturing facility, completed product specification, container, and labelling information.

It is important to assess the effects of changes on the efficacy, effectiveness, and safety of approved products. These changes need to be clearly documented and assessed.

Depending on the magnitude of the impact, some changes may only necessitate the company documenting the change under consideration. Different mechanisms for reporting these changes exist in different jurisdictions, and these can range from an annual report to an supplement filling.

In order to follow the proper compliance procedures, manufacturers should consult the guidance documents specific to the jurisdiction.

The following are the reporting categories for changes made after an approval as per the USFDA:

3.4 Various post approval changes as per USFDA

The guidance defines:

1) Levels of change

2) Tests for controls, manufacturing, and chemistry that are advised for each level of change

3) For every level of change, in vivo bioequivalence testing or in vitro dissolution tests.

Table 1. Various post approval changes as per USFDA (17-21):

The various post approval changes are observed	
1	Components and composition
2	Manufacturing sites
3	Manufacturing process
4	Specifications
5	Container closure system
6	Labelling
7	Miscellaneous changes and
8	Multiple related change

Documentation that should support the change. The FDA may determine that changes submitted in a "changes being effected supplement" [21 CFR 314.70 (c)] are not acceptable after reviewing the supplemental data.

In order to ensure continued product quality and performance characteristics of an instant release solid oral dose formulation for specific post approval adjustments, this guidance outlines application information that should be supplied to CDER.

1) Site Changes- Site modifications only apply to manufacturers under contract with the corporation, as well as they do not include scale-up changes, manufacturing process or equipment changes, component or composition changes, or adjustments to components or composition. The guidance's Section V addresses scaling up. A successful current Good Manufacturing Practices (cGMP) inspection should be completed at new manufacturing facilities.

A. Level 1 Changes

Defined: Level 1 modifications are those that take place at an identical equipment and standard operating procedures are used in a single facility (SOPs), environmental controls (such as temperature and

humidity), and personnel are used. In addition, the production batch records remain unchanged.

Testing Records

a. Aside from what is necessary for application/compendial release, there is no chemistry documentation.

b. Beyond application/compendial release criteria, there is no documentation required for dissolution.

c. There is no documentation for in vivo bioequivalence.

Filing Documentation-Annual report

B. Level 2 Changes

Definition: Level 2 changes include moving locations within a single campus or between buildings on adjacent city blocks, provided that both manufacturing sites continue to use the same equipment, SOPs, environmental controls (such as temperature and humidity), and personnel, and that no other changes are made to the manufacturing batch records other than to the facility's administrative details.

Testing Records

a) Documentation for Chemistry Address of the new site and the most recent batch records. None above what is necessary for application/compendial release.

b) Long-term stability information from one batch were reported in the annual report.

c) Documentation of the Dissolution None beyond what is necessary for application and compendial releases.

d) There is no documentation for in vivo bioequivalence.

Documentation Filing

Supplement with changes being made; annual report (long-term stability test results).

C. Level 3 Changes

Definition: A move in manufacturing location to another campus is included in level 3 alterations. A distinct campus is one where there are no facilities located on the same original contiguous site or on surrounding city blocks. The manufacturing process at the new location must use the same tools, SOPs, environmental factors, and controls to qualify as a Level 3 change. Additionally, manufacturing batch records may not be altered other than for details on administration, directions, and a language translation as necessary.

Test Documentation

Documentation for Chemistry Address of the new site and the most recent batch records. requirements for application/compendial releases.

Stability: a significant volume of data is readily available: One batch on accelerated stability data for three months was provided in a supplement, and one batch on long-term stability data was reported in an annual report.

Important body of information unavailable: Three batches of accelerated stability data for three months may be published in a supplement, and three batches of long-term stability data may be reported in an annual report.

A multipoint dissolution profile should be carried out in the application/compendia medium at 15, 30, 45, 60, and 120 minutes, or until an asymptote is attained, according to Dissolution Documentation Case B. The drug product's dissolving profile at the existing and suggested sites ought to be comparable.

Documentation for in vivo bioequivalence is inadequate.

Documentation Submission: Annual Report (Long-Term Stability Data); Changes Being Effected Supplement.

II. Batch Size Modifications (Scale-Up/Scale-Down) *(22-23)*

The application must include extra information if the size of a batch after approval is changed from the pivotal/pilot scale bio batch material to bigger or smaller production batches. This recommendation does not apply to scale-downs below 100,000 dose units. All scale-up modifications should be thoroughly vetted and, if necessary, inspected by authorised agency staff.

A. Level 1 Changes

Definition of Level: Up to and including a 10x increase in batch size from the pilot/bio batch, provided that:

1) The machinery used to make the test batch follows the same operational principles and design;

2) The batch was produced in full compliance with CGMPs;

3) The test batch and the full-scale production batch both use the same standard operating procedures (SOPs), controls, formulation, and manufacturing techniques.

Test Documentation

Requirements for compendial release of chemistry documentation. amend batch records and submit notification of change in annual report. In the yearly report, one batch on long-term stability was mentioned.

Dissolution Documentation -None above what is necessary for application/compendial release.

In Vivo Bioequivalence-None

Filing Documentation- Annual report with data on long-term stability

B. Level 2 Changes

1. Definition of Level Changes:

Increases in batch size that are greater than ten times that of the pilot or biological batch

1) The equipment used to make the test batch follows the same operational principles and design;

2) The batch was produced in complete accordance with CGMP'S.

3) The test batch and the full-scale production batch both use the same SOPs, controls, formulation, and manufacturing processes.

2. Test Documentation

A. Requirements for the Compendial Release of Chemistry Documents. notification of the modification and the altered batch records.

Testing for stability: two batches, one testing for long-term stability and the other testing for accelerated stability over three months.

Testing of Dissolution Documentation-Case B.

Bioequivalence in vivo: None

3. Submitting Documents

Supplement with changes being made and annual report (long-term stability data).

III. Manufacturing

Equipment utilised in the manufacturing process as well as the process itself may be affected by changes in production.

A. Equipment

1. Definition of Level Changes:

The Meaning of Change 1) Converting non-mechanical or non-automated equipment to mechanical or automated equipment to transfer ingredients.

2) Replace existing equipment with substitutes that have the same design and operation principles and either the same or a different capacity.

2. Test Documentation

i. Chemistry documentation application/ compendial release requirements.

Notification of the change and submission of the revised batch

One batch was subjected to long-term stability testing.

ii. Documentation of Dissolution None above what is necessary for application/compendial release.

iii Documentation for in vivo bioequivalence is inadequate.

3. Annual report submission- (long-term stability data)

2. Level 2 Changes

a. Definition of Level: a change in the equipment's design and operational philosophies.

b. Test Documentation

i. Chemistry Documentation Application/ compendial release requirements

Notification of the modification and batch records that have been modified. Testing for stability: a sizable volume of data is readily available: One batch on accelerated stability data for three months was provided in a supplement, and one batch on long-term stability data was reported in an annual report. Important body of information unavailable: Three batches of accelerated stability data for three months may be published in a supplement, and three batches of long-term stability data may be reported in an annual report.

ii. Case C Dissolution Profiling Documentation

iii. In Vivo Bioequivalence Documentation- None

c. Documentation Filing Annual report-

(long-term stability data); prior permission supplement with reason for changes.

B. Process 1. Level 1 Changes

A Definition of Level- Changes to mixing times and operating speeds that fall within application/validation ranges fall under this category.

b. Test Documentation

i. Documentation for Chemistry None above what is necessary for application/compendial release.

ii. Documentation of Dissolution None above what is necessary for application/compendial release.

iii. In Vivo Bioequivalence Documentation- None.

c. Filing Documentation-Annual report

2. Level 2 Changes

a. Definition of Level- Process adjustments in this category include those that affect mixing durations and operating speeds outside of application and validation ranges.

b. Test Documentation

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

Stability testing: One batch on long-term stability.

ii. Case B's dissolution profile from the dissolution documentation.

iii. Documentation for in vivo bioequivalence is inadequate.

c. Filing Documentation- Changes being effected supplement; annual report (long term

stability data).

3. Level 3 Changes

a. Definition of Level -This category includes modifications to the manufacturing process, such as switching from wet granulation to dry powder direct compression.

b. Test Documentation

i. Requirements for compendial release of chemistry documentation. Notification of the modification and batch records that have been modified. Testing for stability: a sizable volume of data is readily available: One batch of data on accelerated stability for three months was given in the supplement, and one batch of data on long-term stability was reported in the annual report.

Important body of information unavailable: Three batches of accelerated stability data for three months may be published in a supplement, and three batches of long-term stability data may be reported in an annual report.

ii. Dissolution Documentation - Case B dissolution.

iii. In Vivo Bioequivalence Documentation In vivo bioequivalence study. The bioequivalence

Study may be waived if a suitable in vivo/in vitro correlation has been verified.

c. Filing Documentation

Annual report (long-term stability information); prior approval supplement with reason.

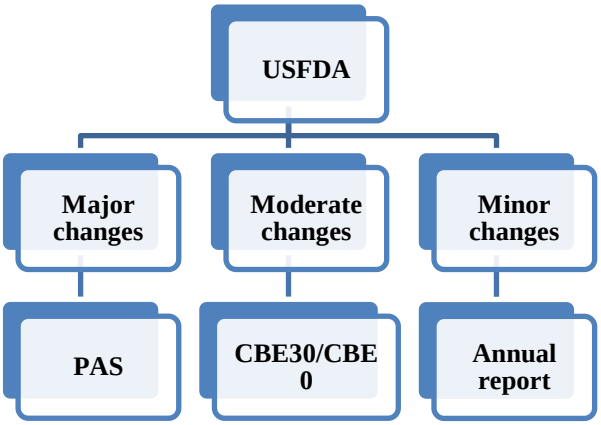

Figure 3. Post Approval Changes As per USFDA (10,11,23)

Table 2. Classification of post-approval changes

Types of Changes	Rules	Types of Applications
Major Changes	21 CFR 314.70(b)	Prior Approval Supplement
Moderate Change	21 CFR 314.70(c)(5)	Changes Being Effected in 30 days
	21 CFR 314.70(c)(6)	Changes Being Effected
Minor Change	21 CFR 314.70(d)	Annual Report / Notification

3.5 General information contained in supplement

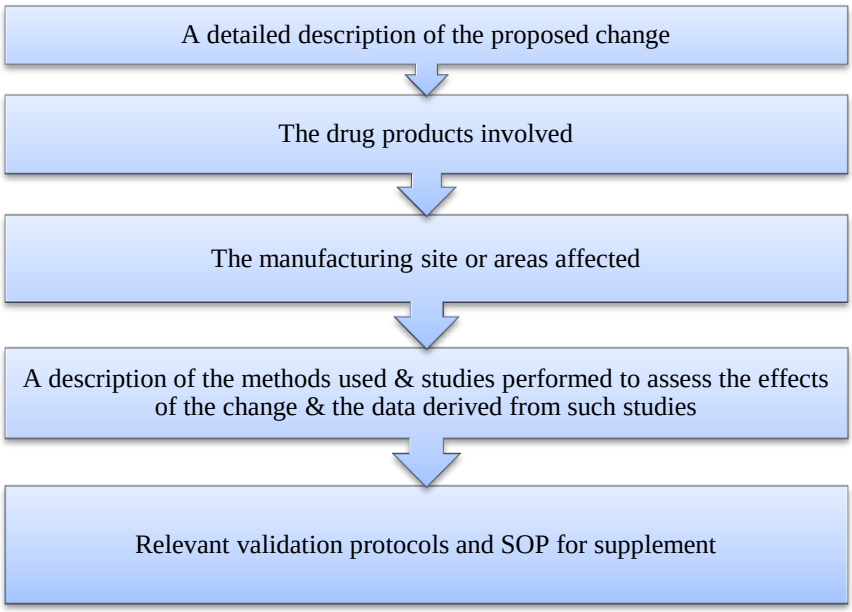

Figure 4. General supplemental information (23-25)

In-Vitro Dissolution

Specifications for general dissolution can be found in section 711 of the most recent United States Pharmacopeia/National Formulary. Each profile should be performed on a minimum of 12 different dose units.

Dissolution profiles may be compared using the following equation that defines a similarity factor (f2): f2 = 50 LOG {[1+1/n (R-T)] x100} n 2 -0.5 t=1 t t where Rt and Tt are the percent dissolved at each time point. An f2value between 50 and 100 suggests the two dissolution profiles are similar.

In-Vivo Bioequivalence Studies

It is only meant to serve as a general outline, and the design of the actual study may change depending on the medication and dose type. Other design considerations include the choice of patients, process, constraints, blood collection, and analytical method.

3.6 Post approval changes as per USFDA

Here in the United States, post-approval changes are referred to as Scale Up and Post-approval changes, and they are classified into three levels.

3.6.1 Major change (prior approval supplement) *(26-30)*

Introduction to PAS

- A Prior approval is required a supplement is necessary when a CMC modification has the potential to have a significant (major) negative impact on the product's identity, strength, quality, purity, or potency as they pertain to its safety or effectiveness. Its name is self-explanatory, which means that the FDA must approve the change before the drug product integrating it can be distributed for patient use.
- Based on the potential risk to products identity, strength, quality, purity or potency, post approval CMC changes includes prior approval supplement.
- A Prior Approval Supplement may be required to be granted as quickly as feasible in the interest of public health (e.g., medicine shortages) or if a delay in implementation would cause the drug manufacturer significant hardship.
- In certain cases, the applicant has the option of requesting an expedited review of the supplement. Prior Approval Supplement-Expedited Review Requested should be clearly identified on the supplement, and an explanation for the request Should be a part of the cover letter.
- Major post-approval CMC modifications in the production procedure, quality assurance measures, machinery, or facilities are summarized in a Prior Approval Supplement (PAS). It necessitates submission both to the FDA and subsequent evaluation and approval by the agency, before the drug product created with the change can be distributed (according to 21 CFR 601.12 (b) (3) and 314.70 (g)

Table 3. Post approval regulatory requirement (PAS) (31-34)

Prior Approval Supplement	
Manufacturing Site	A relocation to a different manufacturing facility, excluding one used to produce or process a drug substance intermediate, when the new facility has never undergone an FDA inspection for the type of operation being moved or when the relocation causes a restart at the new facility of a facility type that has been shut down for more than two years.
	A move to another manufacturing facility, excluding one that produces or processes drug substance intermediates, when the new facility requires an acceptable CGMP inspection for the operation being transferred.
	A move to a different manufacturing location for (1) the manufacture, processing, or primary packaging of drug products when the dose delivered to the patient is regulated by the primary packaging components or when the formulation modifies the rate or extent of availability that drug, or (2) the manufacture or processing of in-process materials with modified-release properties.
	Transferring the production of an aseptically processed sterile drug substance or sterile drug product to a facility or area that is either (1) newly built or renovated or (2) already exists but does not currently produce similar (including container types and sizes) approved drug products
Manufacturing process	Changes such as adding or removal of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form may influence the controlled (or modified) release, metering, or other properties (such as dose (particle size) administered to the patient.
	Modifications to viral or unexpected agent elimination or inactivation techniques. alterations to the cell line or source material (such as a microbe or plant) in the case of drug substance and drug product. Drug compounds and drug products will soon have a new master cell bank or seed. .
	changes that could impact the sterility assurance of the medication.
	A change in the drug substance's synthesis or manufacturing that could have an effect on its impurity profile or any of its physical, chemical, or biological properties.
Specification	lowering an acceptance threshold

	Deleting any part of a specification
	Change outside the approved specification limits range
Container closur system	For liquid and semisolid dosage forms, a modification in the principal packaging components' polymeric materials
	For liquid and semisolid dosage forms, a modification in the principal packaging components' polymeric materials For liquid and semisolid dosage forms in permeable or semipermeable container closure systems, a switch from an ink or adhesive that has been used on the permeable or semipermeable packaging component to an ink or adhesive that has never been used in an approved drug product of the same dosage form, same route of administration, and with the same type of permeable or semipermeable packaging component.
	A change to the major packaging elements of any medication product where those elements regulate the dose administered to the patient.
	Any modification to sterile medicinal items that could compromise sterility assurance, such as: A change from a glass ampule to a glass vial with an elastomeric closure. a switch from another container system to a flexible container system (bag). a switch from a different container system to a prefilled syringe dose form. a switch from a system with a single dose container to one with many dose containers. Changes to container closing systems that add or remove silicone treatments Modifications to a sterile drug product's container's size and/or shape.
	Removal of a secondary packaging element intended to increase protection for the drug product or addition of a secondary packaging element whose makeup may affect the impurity profile of the drug product.
	A switch to a new container closing system if the latter does not offer equivalent or superior protective qualities to the previously approved method.
Labelling	Labelling modifications bring on by new indications and usage, as well as adjustments based on the findings of post-marketing studies.
	Pharmacoeconomic claims are modified or added based on clinical investigations.
	Modifications to the clinical pharmacology or clinical trial sections that take into account new or updated data.
	Modifications based on information from preclinical investigations
	Modification of the labelled storage circumstances
Miscellaneous changes	addition of a comparability or stability protocol
	Modifications to a comparability or stability protocol that has been approved
	An extension of the date of expiration based on (1) information collected utilizing a new or updated stability testing technique that hasn't been approved in the application or (2) complete shelf-life information on pilot scale batches using a protocol that has been approved.

3.6.2 CBE-0 labelling change (35-37)

In the abbreviated new drug application (ANDA), labelling is made based on the FDA notification under "Safety labelling change notification". This notification is received from the FDA's agency for making change in the ANDA labelling when RLD labelling changes occurs.

After receiving notification letter for "labelling change" from the FDA's agency applicant holder submits a supplement that includes "changes being effected (CBE-0)" Also, the submission of supplement is based on the updation of RLD labelling for making generic labelling with the RLD labelling.

Labelling includes some key points are as follows:

a) Font Size for labelling should be not less than 4, for package inserts should be 12 and for medication guide it should be not less than 10.

b) For prescribing information for labelling includes, imprinting ink & gelatin shells in SPL product data element section. As per agency the established name drug product is considered and a common noun and need not to be capitalized unless required by sentence structure. All brand names and trademarks of their respective owners should be their wherever applicable.

c) For the container closure for labelling includes, decrease the medication errors and the expression of strength should be highlighted. addition of control substance symbol as applicable. relocate the company logo to downside, wherever applicable. also increase the prominence of the established name by increasing the font size.

d) For blister label for labelling includes, always write quantity Unit-dose for capsules/Tablets on carton label instead by writing for blister packaging configuration. Also write statement for label for where the label is made.

Table 4. Change being supplemented (CBE-0)

Change being supplemented (CBE-0)	
Manufacturing Site	A move of the final intermediate's production or processing to a separate manufacturing site.
Manufacturing process	A change to procedures or checks that increases assurance
	Elimination of in-process filtration for sterile drug products
Specification	Addition of new test and limits
	specification parameter addition or modification as a result of a quality or safety concern
	Elimination of a minor specification parameter
Container closure system	A change to the shape or size of a non-sterile drug product container without changing the container's closing system
	Except for solid dosage forms, a non-sterile pharmaceutical product in a multiple-unit container that contains a different quantity than what is specified on the label (e.g., grammes, millilitres). .
	A modification, addition, or removal of a desiccant
Labelling	adding an adverse result based on by information given to the applicant or the agency
	adding a safety measure that was inspired by a post-marketing investigation.
	To ensure effective administration of the drug product, the administration statement needs to be clarified.

3.6.3 Minor change (Annual Report) *(38-39)*

a) 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.

b) Annual Report is the report of all changes like chemistry manufacturing control changes, labelling, clinical, non-clinical, distribution data of the drug's component.

c) According to 21 CFR 314.81(2) (other post marketing reports) requires the annual report to be submitted on a regular basis. An applicant must describe minor changes in its next annual report.

d) It serves as a channel for giving updates on non-supplemental post approval commitments (e.g., stability updates) and serves as a reporting method for changes that are judged to have limited Possibility of adversely affecting the medication product from a CMC standpoint.

e) Minor post approval CMC modifications in the production procedure, quality assurance measures, equipment, or facilities are documented in an AR, which is filled every year within 60 days of the anniversary date of approval of the US approval data of the application.

f) If the annual report filling category is deemed inappropriate for the change or additional information is sought to justify the change, FDA has the power to disagree with the modification made within the yearly report and require the distribution of a supplemental application.

g) The annual report must be accompanied by one copy of form-2252 and other relevant documents. Also form 483 is their get issued by the FDA agency to the firm when any objectionable condition is seen by the FDA reviewer during an inspection. 483 include information regarding corrective action of the firm.

Table 5. Post approval regulatory requirement (annual report)

(Annual Report)	
Manufacturing Site	a change in the location of the secondary packaging facility
	a change in the manufacturing site for the labelling
	moving the manufacture of drug ingredient intermediates other than the final intermediate to a separate manufacturing location
	When the procedure is not materially different from that specified in the approved application, a change may be made to the contract sterilization site for packaging components.
	The transfer of production of a finished good sterilized by terminal processes to a newly built structure or an existing structure at the same industrial site.
	a change in the manufacturing facility where solid oral dosage form medicinal items are imprinted with ink.
Manufacturing process	variations to equipment with the same design and operation concept and/or variations in scale

	for pharmaceutical products.
	a small modification to the dosage form's existing code imprint.
	On a solid dosage form drug product other than a modified-release dosage form, the addition or removal of a code imprint by embossing, debossing, or engraving.
	In relation to natural protein drug ingredients and natural protein drug products: a shift in production scale during the finishing process without a related change in equipment. replacing existing equipment with new equipment of equivalent design, functionality, and capacity while maintaining the same level of output.
Specification	Tightening of acceptance criteria
Container closure system	a modification to the non-sterile medication product's container sealing system.
	a modification to the size, shape, or composition of a container for a nonsterile solid dosage form
	a change in the quantity of non-sterile solid dosage forms (such as tablets or capsules) or the labelled amount (such as grammes) in a container with multiple units.
Labelling	changes to the design of a box or container's label without a corresponding modification to the labeling's content.
	Editorial changes, such as adding a distributor's name
Miscellaneous changes	a lengthened expiration date based on complete shelf-life information on production batches gathered in accordance with a procedure endorsed in the application.
	Stability protocol modifications, such as the addition of time points or the deletion of time points that are older than the permitted expiration date
	A change from stability storage conditions previously permitted to those suggested in International Conference on Harmonization (ICH) advice
	replacement of a reference panel or standard used internally in accordance with the processes specified in an approved application
	tightening of acceptance criteria for current reference standards to give more assurance of the purity and potency of medicinal products

4. Conclusion

a) It provides information regarding the submissions to be made for a change in its drug approval. It also provides an analysis of the approaches described in the FDA draft guidance and post-approval change management of CMC changes to generic drug products.

b) Also, with the increasing importance of generic drugs in the US pharmaceutical supply chain, the FDA is allocating more resources to ensure the timely evaluation of these post-approval changes.

c) It is also applicants' responsibility to improve submission quality according to risk and science-based principles and to enhance lifecycle management of generic drugs using proper quality metrics (e.g., process capability).

d) For the generic sector to submit high-quality supplements and for the FDA to manage and assess them more effectively, the data reported here in the thesis can serve as a useful reference.

e) Every drug product that is to be marketed commercially must first receive product approval. But still, the post-approval management cycle is responsible for managing the product's remaining life.

f) Several changes have been implemented in response to the agency's requirements as well as the applicant's requirements for the drug product getting approval.

g) According to the post-approval management cycle, all changes to the approved drug product must be reported to the agency in a specific format.

h) The types of changes are described in the thesis based on reporting categories for post-approval changes and a format that is properly documented.

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Conflict of Interest

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