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A REVIEW : THE NEW DRUG APPLICATION AND ABBREVIATED NEW DRUG APPLICATION

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Abstract:

The New Drug Application (NDA) is the vehicle in the United States through which drug sponsors formally propose that the Food and Drug Administration (FDA) approve a new pharmaceutical for sale and marketing. Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA . An abbreviated new drug application (ANDA) is Specifically designed for an approval of generic drug product. Application for products similar to "already approved drugs" in terms of same dosage form, same route of administration, active ingredients and other conditions Such applications were required to show bioequivalence if FDA thought the products have potential bioavailability problem. All approved products both generic and innovator, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).Generic drug applications are termed as "abbreviated" because they are generally not required to include preclinical and clinical data to establish safety and effectiveness.

Keywords: NDA, ANDA, FDA

Introduction :[1,2,3]

For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following 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 it should 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.
- The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged.

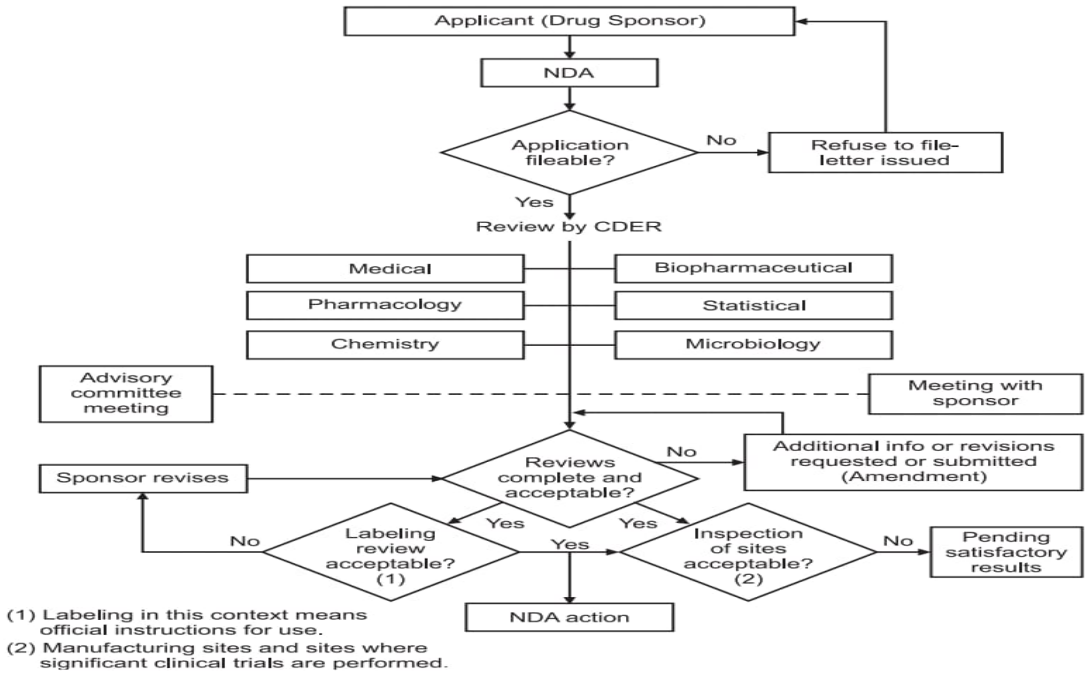

Fig. no.1: New Drug Application (NDA)

An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. All approved products, both innovator and Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product performs in the same manner as the innovator drug. One way applicants demonstrate that a generic product performs in the same way as the innovator drug is to measure the time it takes the generic drug to reach the bloodstream in healthy volunteers. This demonstration of “bioequivalence” gives the rate of absorption, or bioavailability, of the generic drug, which can then be compared to that This demonstration of “bioequivalence” gives the rate of absorption, or bioavailability, of the generic drug, which can then be compared to that of the innovator drug. To be approved by FDA, the generic version must

deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

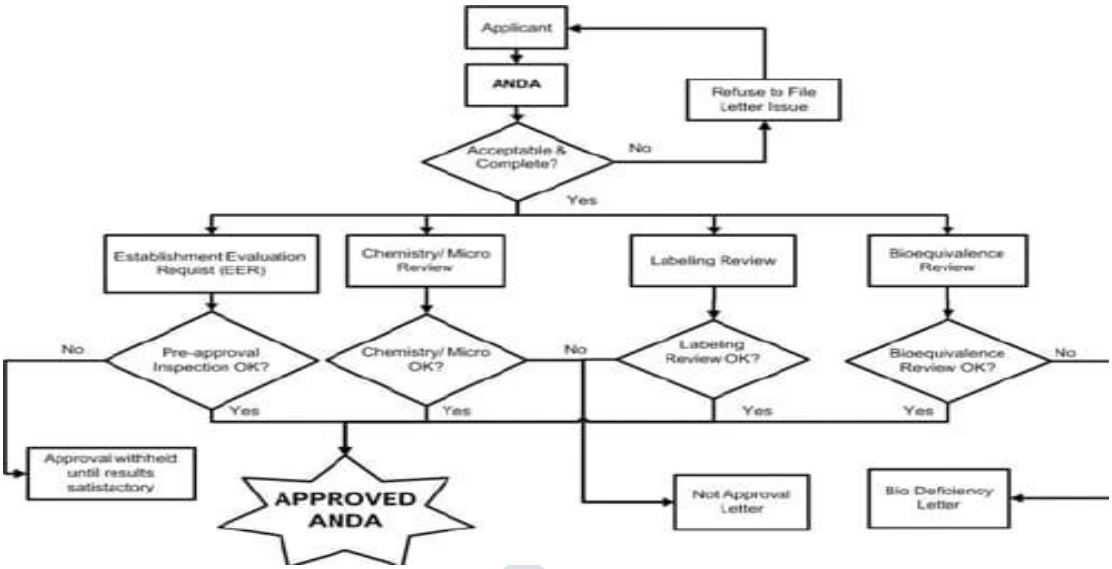

Fig.no.2: ANDA Reviewing Process.

The "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Hatch-Waxman Amendments, established bioequivalence as the basis for approving generic copies of drug products. These Amendments permit FDA to approve applications to market generic versions of brand-name drugs without repeating costly and duplicative clinical trials to establish safety and efficacy. Under the Hatch-Waxman Amendments, brand-name companies gained patent term extension to account for the time the patented product is under review by FDA and also gained certain periods of marketing exclusivity. In addition to the ANDA approval pathway, generic drug companies gained the ability to challenge patents in court prior to marketing as well as 180-day generic drug exclusivity. ANDA approval pathway, generic drug companies gained the ability to challenge patents in court prior to marketing as well as 180-day generic drug exclusivity.

- Requirements and Resources for Approved ANDAs
- Resources for ANDA Submissions
- Guidance Documents for ANDAs
- Laws, Regulations, Policies, and Procedures
- Additional Resources

The following resources provide summaries on NDA and ANDA content, format, and classification, plus the ANDA and NDA review process:[4,5,6]

The following resources provide summaries on NDA content, format, and classification, plus the NDA review process:

Resources for NDA Submissions

The following resources have been gathered to provide you with the legal requirements of a new drug application, assistance from CDER to help you meet those requirements, and internal NDA review principles, policies and procedures.

Guidance Documents for NDAs

Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants/sponsors to provide guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office. For the complete list of CDER guidances, please see the Guidance Index. For information on a specific guidance document, please contact the originating office.

Guidance documents to help prepare NDAs

- Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs and General Considerations.
- Changes to an Approved NDA or ANDA
- Changes to an Approved NDA or ANDA: Questions and Answers
- Container Closure Systems for Packaging Human Drugs and Biologics
- Format and Content of the Microbiology Section of an Application ,
- Format and Content of the Clinical and Statistical Sections of an Application
- Summary for New Drug and Antibiotic Applications--Format and Content of the Summary for New Drug and Antibiotic Applications.
- Formatting, Assembling and Submitting New Drug and Antibiotic Applications,

Guidance for submitting supporting documentation in drug applications for manufacture of drug products:[7,8]

- NDAs: Impurities in Drug Substances
- Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application
- Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application
- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
- Drug Master Files: Guidelines
- FDA IND, NDA, ANDA, or Drug Master File Binders

PET Drug Applications - Content and Format for NDAs and ANDAs — 2011

Laws, Regulations, Policies and Procedures

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. With numerous amendments, it is the most extensive law of its kind in the world. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code Of Federal Regulations (CFR)

The final regulations published in the Federal Register (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the CFR. The CFR is divided into 50 titles which represent broad areas subject to Federal regulations. The FDA's portion of the CFR interprets the Federal Food, Drug and Cosmetic Act and related statutes. Section 21 of the CFR contains all regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

- 21CFR Part 314 - Applications for FDA Approval to Market a New Drug or an Antibiotic Drug.

CDER's Manual of Policies and Procedures (MaPPs)

These documents are approved instructions for internal practices and procedures followed by CDER staff to help standardize the new drug review process and other activities. MaPPs define external activities as well. All MaPPs are available for the public to review to get a better understanding of office policies, definitions, staff responsibilities and procedures.

MAPPS of particular interest to NDA applicants

- Review of the Same Supplemental Change to More than One NDA or ANDA in More Than One Review Division
- NDAs and BLAs: Filing Review Issues
- Action Packages for NDAs and Efficacy Supplements
- Refusal to Accept Application for Filing From Applicants in Arrears
- Requesting and Accepting Non-Archivable Electronic Material for CDER Applications

Prescription Drug User Fee Act (PDUFA)

On November 21, 1997, The President signed the Food and Drug Administration Modernization Act of 1997. This legislation includes authorization for FDA to continue to collect three types of user fees from applicants who submit certain new drug and biological product applications. FDA was first authorized to collect user fees under the Prescription Drug User Fee Act (PDUFA) of 1992.

- Prescription Drug User Fee Act Related Documents

NDA Forms and Electronic Submissions

- Form FDA-356h. Application to Market a New Drug, Biologic, or An Antibiotic Drug For Human Use
  - Form FDA-356h instructions
- Form FDA-3397. User Fee Cover Sheet
- Form FDA-3331. New Drug Application Field Report
- Guidance Documents for Electronic Submissions

Advisory Committees:[9,10]

Advisory committees provide independent advice and recommendations to the FDA on scientific and technical matters related to the development and evaluation of products regulated by the Agency. CDER requests advice from advisory committees on a variety of matters, including various aspects of clinical investigations and applications for marketing approval of drug products. Committee members are scientific experts such as physician-researchers and statisticians, as well as representatives of the public, including patients. Although the committees provide recommendations to the Agency, final decisions are made by FDA.

- FDA Advisory Committees
- CDER Advisory Committees
- CFR 21 Part 14 Public Hearing Before a Public Advisory Committee. Detailed description of advisory committees from the Code of Federal Regulations.
- Guidance for Industry: Advisory Committees. Includes information on membership, conflict of interest, scheduling, and action on recommendations.
- Advisory Committee Meeting Calendar. Several dates have been set aside by CDER advisory committees for possible future meetings. The subject matter and location of the meetings (if they are held) will be published in the Federal Register in the month prior to the meeting date.

The following resources provide summaries on ANDA content, format, and classification, plus the ANDA review process:

Resources for ANDA Submissions:

The following resources provide ANDA applicants with the statutory and regulatory requirements of an ANDA application, assistance from CDER to help you meet those requirements, and internal ANDA review principles, policies, and procedures. Summary tables, application forms, and other ANDA submission resources are available in ANDA Forms & Submission Requirements.

Guidance Documents for ANDAs:

Guidance documents represent the Agency's current thinking on a particular topic. These documents provide guidelines for the content, evaluation, and ultimate approval of applications and also to the design, production, manufacturing, and testing of regulated products for FDA review staff, applicants, and ANDA holders.

- Generic Drugs Guidances
- Biopharmaceutics Guidances
- Product-Specific Guidances for Generic Drug Development

Laws, Regulations, Policies, and Procedures:

The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the United States. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code of Federal Regulations:

The final regulations published in the Federal Register (a daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the Code of Federal Regulations (CFR). Section 21 of the CFR contains most of the regulations pertaining to food and drugs. The regulations document most actions of all drug applicants that are required under Federal law. The following regulations directly apply to the ANDA process:

- 21CFR Part 314: Applications for FDA Approval to Market a New Drug
- 21CFR Part 320: Bioavailability and Bioequivalence Requirements

Manual of Policies and Procedures:

CDER's Manual of Policies and Procedures (MAPPs) document internal practices and procedures followed by CDER staff to help standardize the drug review process and other activities, both internal and external. Chapter 5200 covers generic drugs processes and activities.

Additional Resources:

- **Investigational New Drug Application (NDA):** Resources to assist drug sponsors with submitting applications for approval to begin new drug experiments on human subjects.
- **New Drug Application (NDA):** Resources to assist drug applicants with submitting applications for approval to market a new drug.
- **Pharmaceutical Quality Resources:** Resources to help meet compliance with the approval process for new drug applications; includes a review of the manufacturer's compliance with Current Good Manufacturing Practice.

- **Clinical Trials and Human Subject Protection:** Regulations and guidelines for scientists who design and run experiments (clinical trials) to test the safety and effectiveness of new drugs on human subjects.
- **Surveillance: Post Drug-Approval Activities:** FDA's post drug-approval activities to monitor the ongoing safety of marketed drugs by reassessing drug risks based on new data learned after the drug is marketed, and recommending ways of trying to most appropriately manage that risk.
- **Small Business & Industry Assistance Program (SBIA):** CDER's SBIA program offers a variety of multimedia learning resources.

Guidance for Industry Changes to an Approved NDA or ANDA:

I. Reporting categories:

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 . This type of supplement is called, and should be clearly labeled, a Prior Approval Supplement - Expedited Review Requested. FDA is most likely to grant requests for expedited review based on extraordinary hardship for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A moderate change is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a Supplement - Changes Being Effected in 30 Days. 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.

General requirements:

Other than for editorial changes in previously submitted information (e.g., correction of spelling ortypographical 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 . 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. In annual reports, the list should be included in the summary section. The applicant must describe each change fully in the supplement or annual report.

I. Assessing the effect of manufacturing changes:

A. Assessment of the Effects of the Change:

The holder of an approved application under section 505 of the Act must assess the effects of the change

before distributing a drug product made with a manufacturing change (§ 314.70(a)(2)). For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (section 506A (b), (c)(1), (d)(2)(A), and (d)(3)(A) of the Act). The type of information that must be included in a supplemental application or an annual report is specified in (c)(4), and (d)(3).

1. **Conformance to Specifications**

An assessment of the effects of a change on the identity, strength, quality, purity, and potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, and/or drug product affected by the change conform to the approved specifications. A specification is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. Acceptance criteria are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the;

Material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

1.**Additional Testing**

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

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

closure system.

- An applicant should refer to all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change. If guidance for information that should be submitted to support a particular change is not available, applicants can consult the appropriate CDER chemistry or microbiology review staff for advice.

Major Changes (Prior approval supplement):

i. The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

ii. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years.

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

iv. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics. Examples of these types of drug products include modified-release solid oral dosage forms,[15] transdermal systems, liposomal drug products, depot drug products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.

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

b. Moderate Changes (Supplement - changes being effected):

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved (see sections VI.B.1 and 2), then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement.

Supplement - Changes Being Effected in 30 Days;

- A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance.
- For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site except as provided for in section VI.B.4.
- A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form drug products.
- A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the testprocedures have been fulfilled (e.g., providing methods validation.

Minor Changes (Annual Report): The following are examples of changes considered to have a minimal potential to have anadverse effect on the identity, strength, quality, purity, or potency of a drug product as thesefactors may relate to the safety or effectiveness of the drug product. If the new site does not have a satisfactory CGMP inspection for the type of operation being moved, then FDA recommends that the changes listed below (excluding changes relating to drug substance intermediate manufacturing sites) be submitted in a prior approval supplement (see sections VI.B.1 and 2).

A move to a different manufacturing site for secondary packaging;

i. A move to a different manufacturing site for labeling.
ii. A move to a different manufacturing site for the manufacture or processingof drug substance intermediates other than the final intermediate.
iii. 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
iv. 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.
v. A move to a different manufacturing site for the ink imprinting of solid oraldosage form drug products.

I. Manufacturing Process:

a. General Considerations

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

b. Major changes (Prior approval supplement): The following are examples of changes considered to have a substantial potential to havean adverse effect on the identity, strength, quality, purity, or potency of a drug

product as these factors may relate to the safety or effectiveness of the drug product.

1. Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.
2. Changes that may affect drug product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include:

- Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa.
- Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation.
- Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacementsteam process with a process using superheated water spray).
- Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) thatwill come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line.
- Replacing a Class 100 aseptic fill area with a barrier system or isolator foraseptic filling. Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator maybe submitted as a changes-being-effected-in-30-days supplement.
- Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time.
- Changes from bioburden-based terminal sterilization to the use of anoverkill process, and vice versa.
- Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent beyond thevalidated limits in the approved application.
- Changes in sterilizer load configurations that are outside the range ofpreviously validated loads.

Minor changes (Annual report):

- The following are examples of changes considered to have a minimal potential to have anadverse effect on For drug products, changes to equipment of the same design and operatingprinciple and/or changes in scale except as otherwise provided for in thisguidance (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).

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.

I. Specifications

A. General considerations:

All changes in specifications from those in the approved application must be submitted in aprior approval supplement unless otherwise exempted by regulation or guidance. 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 inNDA and ANDA submissions.

II. Container closure system

A. General considerations:

The potential for adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product when making a change to or in the container closure system is generally dependent on theroute of administration of the drug product, performance of the container closure system, and the likelihood of interaction between the packaging component and the dosage form. In some cases there may be a substantial potential for adverse effect, regardless of direct drug product testing for conformance with the approved specification. A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

A. Major changes (prior approval supplement): The following are examples of changes considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.

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

ii. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change from an ink and/or adhesive used on the permeable or semipermeable packaging component to an ink or adhesive that has never been used in a CDER-approved drug product of the same dosage form andsame route of administration and with the same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl

chloride).

iii. A change in the primary packaging components for any drug product when the primary packaging components control[20] the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).

iv. For sterile drug products, any change that may affect drug product sterilityassurance, such as:

- A change to a flexible container system (bag) from another containersystem.
- A change to a prefilled syringe dosage form from another container system.
- A change from a single unit dose container to a multiple dose containersystem.
- Changes that add or delete silicone treatments to container closure systems(such as elastomeric closures or syringe barrels).

B. Moderate changes (supplement – changes being effected):

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as thesefactors may relate to the safety or effectiveness of the drug product.

Supplement - Changes Being Effected in 30 Days

- A change to or in a container closure system, except as otherwise provided for in this guidance, that does not affect the quality of thedrug product.
- Changes in the size or shape of a container for a sterile drugsubstance.
- A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a nonsterile drug product in aunit-of-use container.

Supplement - Changes Being Effected

- A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2),without a change from one container closure system to another.
- A change in the labeled amount (e.g., grams, milliliters) of drug product for a nonsterile drug product in a multiple-unit container, except for solid dosage forms.
- A change in or addition or deletion of a desiccant.

C. Minor Changes (Annual Report):

The following are examples of changes considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as thesefactors 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 protocolapproved in the application or published in an official compendium.
- A change in the size and/or shape of a container for a nonsterile soliddosage form.
- 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 dosageform 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:

D. Labeling:[11,12]

1.General considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. In accordance with , 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) . All labeling changes for ANDA drug products must be consistent with section 505(j) of the Act.

2.Major Changes (prior approval supplement)

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

- Changes based on postmarketing study results, including, but not limited to,labeling changes associated with new indications and usage.
- Change in, or addition of, pharmacoeconomic claims based on clinicalstudies.
- Changes to the clinical pharmacology or the clinical study section reflectingnew or modified data.

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.

- A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocolapproved in the application or published in an official compendium.
- A change in the size and or shape of a container for a nonsterile soliddosage form.
- 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 dosageform 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:
- **Miscellaneous changes:**

  Major changes (prior approval supplement):

  The following are examples of changes considered to have a substantial potential to havean 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.

E. Changes requiring completion of studies in accordance with 21 CFR part320 to demonstrate equivalence of the drug product to the drug product asmanufactured without the change or to the reference listed drug.

F. Addition of a stability protocol or comparability protocol.

Moderate changes (Supplement – changes being effected):

The following are examples of changes considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as thesefactors may relate to the safety or effectiveness of the drug product.

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

ii. **Supplement** - changes being effected No changes have been identified.

- **Multiple related chances:**

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 forthe 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.

Enforcement of pharmaceutical patents in the US2: ANDA PROCESS While filing an ANDA, a generic firm must certify any one of the following: CERTIFICATION INDICATION PARAGRAPH I Patent information on the drug has not been filed in the orange book) PARAGRAPH II Patent has already expired PARAGRAPH III Date on which patent will expire & that the generic drug will not go to the market until that date passes PARAGRAPH IV Patent is invalid & will not be infringed by the manufacturer , use or sale of the generic drug.

Enforcing a patent listed in the orange book:

In case of certification I & II, approval for manufacture can be granted immediately. In case of III, approval of ANDA can be made effective from the date of expiration. In case of IV, it is mandatory for the manufacturer to notify the original patent holder within 20 days, who can take up to 45 days to bring an infringement suit against the manufacturer; if he fills his IPRs are being violated. However, if no such action is taken within the stipulated period, certification of the ANDA applicant will be accepted by the FDA If an infringement action is brought in time, FDA must suspend approval of the ANDA until the date of court's decision. If the court decision goes in favor of the patent owner, FDA will suspend the approval till expiry of the patent. FDA does not wait indefinitely the maximum time available for coming to decision is 30 months(2.5 years) after the expiry of 45 days i.e. filing of a reply by a drug manufacturer within 45 days will result in delay of a minimum of 2.5 years for the generic drug maker.

"Orange book" Listings : Each holder of an ANDA must list relevant patents it believes would be infringed if a generic drug were marketed before expiration of these patents. The FDA maintains a list of these patents & publishes patent information on approved drug products in the Agency's publication Approved Drug Products

with Therapeutic Equivalence Evaluations, also known as the Orange Book. It lists all approved drug products with their therapeutic equivalence codes in addition to the products' patent and exclusivity information The process of-

• Patent certification,

• Notice to the NDA holder and patent owner,

• A 45-day waiting period,

• Possible patent infringement litigation and

The statutory 30-month stay may result in a considerable delay in the approval of ANDAs when an innovator company submits a new patent relisting to FDA. Therefore, ANDA applicants often closely scrutinize these listings 3 .

Time – frame for listing a patent :

The company filing ANDA under para IV must submit full & complete information over & above what is necessary under current law & must notify the patent owner within 20 days after ANDA filing. If patent owner does not file infringement proceeding within 45 days of notification issued by ANDA applicant, the applicant may request for a declaratory judgments & thus avoid being sued. If sued, applicant may file a counter claim requiring patent owner to make changes in the orange book listing. This favors the patent holder, because he does not have to pay any damages for not modifying the orange Book listing in time & there is apparently no time limit for making such modification.

Re-listing / De – listing of a patent FDA's:[13,14]

regulations provide that, in the event of a dispute as to the accuracy or relevance of patent information submitted to and subsequently listed by FDA, an ANDA applicant must provide written notification of the grounds for dispute to the Agency. FDA will then ask the NDA holder to confirm the correctness of the patent information and listing. Unless the patent information is withdrawn (De-listing) or amended (Re-listing) by the NDA holder, FDA does not change the patent information in the Orange Book. If a patent is listed in the ―Orange Book,‖ an applicant seeking approval for an ANDA must submit a certification to the patent. Even an applicant whose ANDA is pending when additional patents are submitted for listing by the sponsor must certify to the new patents, unless the additional patents are submitted by the patent holder more than 30-days after issuance by the U.S. Patent and Trademark Office. Until the final rule effective date, pending generic drug applications may be subject to multiple overlapping 30-month stays if new patents are relisted for the innovator drug and those patents result in litigation. But under Medicare Prescription Drug & Modernization Act of 2003,a very important change in HWA, only one 30 month stay will be permitted i.e. non extension of 30-month statutory period4 .

Pre – Listing due diligence:

Over the past few years, new patents have occasionally been submitted to FDA for listing in the Orange Book shortly before patents already listed in the Orange Book were scheduled to expire. These new patents have been

submitted to FDA within the required 30-days of issuance by the Patent and Trademark Office. If the NDA sponsor complies with the requirements of the statute and regulations in submitting a patent for listing in the "Orange Book," the Agency may not reject a patent merely on the basis that, but for the filing of the patent, ANDAs would be eligible for final approval.

Use of terms and codes for listing 6 reference listed drug (Innovator Drug Product):[15,16]

A reference listed drug (21 CFR 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. BIOAVAILABILITY. The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. PHARMACEUTICALLY EQUIVALENT DRUG PRODUCTS are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling. PHARMACEUTICAL ALTERNATIVES contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths. BIOEQUIVALENT DRUG PRODUCT (GENERIC DRUG PRODUCT) Pharmaceutical equivalent or pharmaceutical alternative products that display comparable bioavailability when studied under similar experimental conditions. STATISTICAL CRITERIA FOR BIOEQUIVALENCE For Bioavailability FDA uses the ±20% test (for generic) i.e. the amount of active ingredient in the blood serum over a period of time has to come within ±20% of that which is observed with the patented drug (of innovator).

FDA classifies as therapeutically equivalent those products that meet the following general criteria:[17,18]

(1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity & identity (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they "A" CODES Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products. "A" products are those for which actual or potential bioequivalence problems have been resolved with adequate in vivo and/or in vitro evidence supporting bio-equivalence.

Drug products designated with an "A" code fall under one of two main policies: (1) for those active ingredients or dosage forms for which no in vivo bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions) or satisfied for solid oral dosage forms by a showing that an acceptable in vitro dissolution standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications

(these are designated AA, AN, AO, AP, or AT, depending on the dosage form, as described below); or (2) for those DESI drug products containing active ingredients or dosage forms that have been identified by FDA as having actual or potential bioequivalence problems, and for post1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through in vivo and/or in vitro studies the bioequivalence of the product to a selected reference product (these products are designated as AB).

Hatch waxman act amended to strike balance between both acts:[19,20]

The HWA was crafted to strike a balance between 2 competing goals (i) stimulation of new drug innovation (ii) cost containment via easier access to lower cost generic alternatives The goal of the act is to balance long term need for research & development of life saving drugs against the relatively short term goal of providing low cost, high quality pharmaceuticals for consumers. 5.1 Patent term restoration up to 5 years for INNOVATOR In fulfillment of the first objective ,the act added section 156, granting branded pharmaceutical companies upto five years of extra patent life to compensatre for time lost due to FDA Regulatory delays.

The idea was to provide innovator drug companies with IPR Protection sufficient to recoup their investment, thus ensuring the financial incentives necessary for continued research & development of new drugs. 5.2 180 Days Exclusive Marketing Rights for first GENERIC applicant At the same time, the act made it easier for generic drugs companies to market their products through the use of an abbreviated new drug application (ANDA).Under this procedure, generic companies were no longer required to duplicate the safety & efficacy testing required of the brand name companies for FDA approval of branded pharmaceuticals. Moreover they are given marketing exclusivity for 180 days to generic drug companies that successfully challenges & spurs competition. Market exclusivity affords generic drug companies the benefit of marketing a generic drug without competition from other generic companies for 180 days. Generic drug companies are able to reap significant profit during this time. Once several competitors enter the market & begin selling the generic, the price typically falls by 75-80 percent.

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