PREPARATION OF NEW DRUG APPLICATION (NDA) / ABBREVIATED NEW DRUG APPLICATION (ANDA) MAJOR AND MODERATE POST-APPROVAL CHANGES FOR PARENTERAL DRUG PRODUCTS SITE TRANSFER

Wilberto Robles Vázquez
Master in Manufacturing Competitiveness

José A. Morales, Ph.D. P.E.
Industrial Engineering Department
Polytechnic University of Puerto Rico

ABSTRACT

Actually, the Food and Drug Administration is the United States Federal Agency responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation. When a pharmaceutical company decides to manufacture a new drug product should submit to the Food and Drug Administration either a New Drug Application or an Abbreviated New Drug Application. After a New Drug Application or Abbreviated New Drug Application is approved by the Food and Drug Administration, any major, moderate, and/or minor regulatory changes must be reported to the Agency. The Food and Drug Administration Guidance for Industry of Changes to an Approved New Drug Application or Abbreviated New Drug Application Chemical Manufacturing Controls Revision 1 of April 2004 will be evaluated and explain major or moderate changes classification. Based on the rigorous evaluation of the Food and Drug Administration for the pharmaceutical manufacturing companies and the wide variety of different post-approval changes, here is developed a step by step guidance to prepare and report a post-approval change supplement.

INTRODUCTION

Food and Drug Administration have the rights to evaluate all post-approval changes and determine recommendations as per section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and § 314.70 (21 CFR 314.70). The content in this article is for informational purposes only and does not intend to supersede the FDA (the Agency) standpoint.

Actually, the FDA is the U.S. Federal Agency responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health [3]. For this reason, all of the critical activities within a pharmaceutical company distributing product in U.S. must comply with all FDA regulations.

When a pharmaceutical company decides to manufacture a new drug product should submit to the FDA either an NDA or ANDA. 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. [6]. An ANDA contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to

provide a safe, effective, low cost alternative to the American public [1].

After an NDA or ANDA is approved by the FDA, any major, moderate, and/or minor regulatory changes must be reported to the Agency. As per FDA Guidance for Industry of Changes to an Approved NDA or ANDA CMC Revision 1 of April 2004 [4], major, moderate, and minor regulatory changes are defined as follows:

- A ***major change*** is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called, and should be clearly labeled, a ***Prior Approval Supplement*** (§ 314.70(b)).
- 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 this change. This type of supplement is called, and should be clearly labeled, a ***Supplement – Changes Being Effected in 30 Days*** (§ 314.70(c)(3)). The drug product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required (§ 314.70(c)(5)(i)). For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change (§ 314.70 (a)(2) and (c)(4). If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amend to provide the missing information (§ 314.70(c)(5)(ii)). FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement (§ 314.70(c)(6)). This type of supplement is called, and should be clearly labeled, a ***Supplement – Changes Being Effected.*** If, after review, FDA disapproves a changes-being-effected-in-30-days supplement or changes-being-effected supplement, FDA may order the manufacturer to cease distribution of the drug products made using the disapproved change (§ 314.70(c)(7)).
- A ***minor change*** is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next ***Annual Report*** (§ 314.70(d)).

Based on the rigorous evaluation of the FDA for the pharmaceutical manufacturing companies and the wide variety of different post-approval changes, there is no step by step guidance to prepare and report a post-approval change supplement.

METHODS

The FDA Guidance for Industry of Changes to an Approved NDA or ANDA CMC Revision 1 of April 2004 [4] will be evaluated to explain major or moderate changes classification. This explanation pretend to describe some possible interpretations made to the FDA Regulatory Guidance.

Since there is no specific guidance to prepare an effective post-approval supplement, a proven example of how a parenteral drug product manufacturing site transfer major or moderate post-approval change could be reported to the Agency will be discussed. This example is based on the Module 3 of the International Conference on

Harmonization (ICH) Common Technical Document (CTD) recommended format [5].

RESULTS

[4] The CDER (Center for Drug Evaluation and Research) must be notified when a manufacturer changes to a manufacturing site that is different from those specified in the approved application (314.70(a)). FDA recommends that the supplement or annual report identify whether the proposed manufacturing site is an alternative to or replacement for the site or sites provided for in the approved application. FDA recommends that a move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, be submitted as a prior approval supplement if the site does not have a ***satisfactory CGMP inspection*** for the ***type of operation*** being moved.

- 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.
    - 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.
    - 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.
    - 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, transdermal systems, liposomal drug products, depot drug products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.
    - Transfer of the manufacture of an aseptically processed sterile drug substance or aseptically processed sterile drug product to (1) a newly constructed or refurbished aseptic processing facility or area or (2) an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved drug products. An example would be transferring the manufacture of a lyophilized drug product to an existing aseptic process area where no approved lyophilized drug products are manufactured or where the approved lyophilized drug products being manufactured have different container types and/or sizes than the container of the drug product being transferred.
    - Transfer of the manufacture of a finished drug product sterilized by terminal process to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility similar drug product types and processes may be submitted as a changes-being-effected-in-30-days supplement.
- 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 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.

- 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 from 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 post approval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing method validation samples), and (3) the new testing facility has the capability to perform the intended testing.
- Supplement – Changes Being Effected
  - A move to a different manufacturing site for the manufacture or processing of the final intermediate.

In order to standardize the format of the post-approval supplements to be submitted to the FDA, the ICH guidance to prepare documents in CTD format can be used to include the necessary information to submit a successful supplement. Table 1 shows the Module 3 of the ICH CTD recommended format [5]:

Table 1: *Module 3 ICH CTD recommended format*

Section	Content
3.1	Table of Content
3.2	Body Data
3.2.S	Drug Substance
3.2.S.1	General Information
3.2.S.2	Manufacture
3.2.S.3	Characterization
3.2.S.4	Control of Drug Substance
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability
3.2.P	Drug Product
3.2.P.1	Description and Composition of the Drug Product
3.2.P.2	Pharmaceutical Development
3.2.P.3	Manufacture
3.2.P.4	Control of Excipients
3.2.P.5	Control of Drug Product
3.2.P.6	Reference Standards or Materials
3.2.P.7	Container Closure System
3.2.P.8	Stability
3.2.A	Appendices
3.2.A.1	Facilities and Equipment
3.2.A.2	Adventitious Agents Safety Evaluation
3.2.A.3	Novel Excipients
3.2.R	Regional Information
3.3	Literature References

DISCUSSION

As explained in Results section, there are a wide variety of major and moderate changes within a site to site transfer change and all of them can be classified within the mentioned classifications. The most important thing to prepare an effective post approval supplement is the correct classification. If the FDA fined that the classification was wrong, they will refuse the evaluation of it. If there are doubts in the correct classification, a phone call to the Agency could be a good approach.

After making a correct classification of the nature of the site to site transfer change; there are several information that must be provided to prepare the post-approval supplement. Reporting with a clear writings and self explained documents is the key to avoid deficiencies given by the FDA.

Now there is an example of a successfully Prior Approval Supplement submitted for a site to site parenteral drug product transfer of an ANDA based on the Module 3 of the ICH CTD recommended format [5]. This is a real example of a change that was classified as Major (Prior Approval Supplement) and submitted to the Agency without deficiencies.

- A cover letter with a summary and intention of the supplement must be at the beginning of the package and directed to the Director of the Office of Generic Drugs. A field copy letter with the true and complete supplement must be sent to the Company Headquarters FDA District Office. A courtesy field copy letter with the true and complete supplement should be sent to the proposed manufacturing site FDA District Office.
- A detailed Table of Content (Including: Sections, Attachments, Appendices, Figures, Diagrams, Protocols, Reports, Literature Cited, etc.) must be included with page numbers.
- A form FDA 356h must be filled with details of submission [2].
- Chemical Manufacturing and Controls (CMC) Section.
  - A submission summary including but not limited to the following:
    - Report flow information.
    - Supplement intention.
    - Drug Product information (strength, concentration, fill volume, etc.)
    - Exhibit Batch information (stability information, date of manufacturing, conditions, size, etc.)
  - A certification of the field copy must be signed by the Company Regulatory Affairs management.
  - A detail description of the new manufacturing site facilities including address, facilities and capabilities (supporting drawings as well).
  - Information of U.S. Agent (if any), Corporate Headquarters Offices including address.
  - CGMP Certification given by Quality Department and Debarment / List of Convictions Certification given by the Human Resources Department.
  - Detail narrative description of the new manufacturing site process (manufacturing flow chart, processing time limits, bulk hold time, reprocessing statement, control numbers for raw material, and control numbers for finished drug product).
  - Comparison between the originating manufacturing site process and the new manufacturing site process.
  - Comparison between the exhibit batch and the proposed commercial batch.
  - Blank batch record for proposed commercial batch in the new manufacturing facility.
  - Material contact studies report, filter compatibility screening report, product

bubble point ratio determination report, bacterial filter retention study report, and microbiological methods validation report.

- New manufacturing site in-process controls (testing laboratories addresses and manufacturing sites addresses.
- Summary of information (name, lot, vendor, expiry, data, USP monograph (if applicable), etc.) for all of the Raw Material (including API) used for the manufacturing of the exhibit batch.
- Summary of information (name, lot, vendor, expiry, data, etc.) for all of the packaging components (vials, stoppers, and seals) used for the manufacturing of the exhibit batch.
- Finished drug product testing data for exhibit batch.
- Executed exhibit batch record.
- Stability data for exhibit batch up to 3 months.
- Post-approval stability testing schedule.
- Post-approval commitments.

- Sterility Assurance Section
  - Description of Building and Facilities.
    - Floor Plan.
    - Location of Equipment.
  - Description of the Overall Manufacturing Operation.
    - Drug Product Solution Filtration.
    - Specification Concerning Holding Periods.
    - Critical Operations.
  - Description of the Sterilization and Depyrogenation of Containers, Closures, Equipment and Components.
    - Bulk Drug Solution Components that are Sterilized Separately.
    - Sterilization Information in the Batch Records.
  - Description of the Procedures and Specifications for Media.
    - The Filling Room.
    - Container-Closure Type and Size.
    - Volume of Medium Used in Each Container.
    - Type of Medium Used.
    - Number of Units Used.
    - Number of Units Incubated.
    - Number of Units Positive.
    - Incubation Parameters.
    - Date of Each Media Fill.
    - Simulation.
    - Microbiological Monitoring.
    - Process Parameters.
  - Actions Concerning Product When Media Fills Fail.
  - Microbiological Monitoring of the Environment.
    - Microbiological Methods:
      - ❖ Airborne Monitoring.
      - ❖ Surface Monitoring.
      - ❖ Microorganisms in Personnel.
      - ❖ Water Systems.
      - ❖ Product Component Bioburden.
    - Yeasts, Molds, Anaerobic Microorganisms.
    - Exceeded Limits.
  - Container-Closure and Packaging Integrity.

- Sterility Testing Methods and Release Criteria.
- Bacterial Endotoxin Test and Method.
- Evidence of Formal Written Procedures.

- Maintenance of Microbiological Control and Processes.
  - Container Closure Integrity.
  - Preservative Effectiveness.
  - Endotoxin Testing.
- Literature Cited.
- List of Appendices.

Following the aforementioned example with a correct classification of the nature of the site to site change, an effective post approval ANDA supplement can be submitted to the Agency.

REFERENCES

[1] *Abbreviated New Drug Application (ANDA) Process for Generic Drugs*. (n.d.). Retreived December 25, 2008, from http://www.fda.gov/CDER/REGULATORY/APPLICATIAPP/anda.htm

[2] *Application to Market A New Drug, Biologic, or an Antibiotic Drug for Human Use* (n.d.) Retreived January 14, 2009, from http://www.fda.gov/opacom/morechoices/fdaforms/356Hes.pdf

[3] *FDA's Mission Statement*. (n.d.). Retrieved January 6, 2009, from http://www.fda.gov/opacom/morechoices /mission.html

[4] *Guidance for Industry Changes to an Approved NDA or ANDA*. (n.d.). Retreived December 25, 2008, from http://www.fda.gov/CDER/guidance/3516fnl.pdf

[5] *Guidance for Industry M4Q: The CTD - Quality*. (n.d.). Retreived January 14, 2009, from http://www.fda.gov/cder/guidance/4539q.pdf

[6] *New Drug Application (NDA) Process*. (n.d.). Retrieved January 6, 2009, from http://www.fda.gov/CDER/REGULATORY/APPLICATIAPP/nda.htm

Wilberto Robles Vázquez se graduó del programa de Maestría en Manufactura Competitiva, en la colación de grados de 2009. El señor Robles posee un grado de bachillerato en Microbiología y sus intereses en investigación van alineados al área de Procesos Farmacéuticos.